Audet 10_531533 - - History

Ø None found w/ Spec.

(DB ✓ again on next action)

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L7            125 SEA SUB=L5 SSS FUL L6

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L17            15 SEA ABB=ON  PLU=ON  "CUEVAS M"/AU OR ("CUEVAS MARCHANTE
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L18             1 SEA ABB=ON  PLU=ON  L16 AND L17
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                  D STAT QUE L20
                  D IBIB ABS HITSTR L20 1-58


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   26 SEP 2006  HIGHEST RN 908803-03-2
     DICTIONARY FILE UPDATES:  26 SEP 2006  HIGHEST RN 908803-03-2

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     REGISTRY includes numerically searchable data for experimental and
     predicted properties as well as tags indicating availability of
     experimental property data in the original document.  For information
     on property searching in REGISTRY, refer to:

     http://www.cas.org/ONLINE/UG/regprops.html

     FILE HCAPLUS

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FILE COVERS 1907 - 27 Sep 2006 VOL 145 ISS 14
FILE LAST UPDATED: 26 Sep 2006 (20060926/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 27 Sep 2006  VOL 145 ISS 14
FILE LAST UPDATED: 26 Sep 2006  (20060926/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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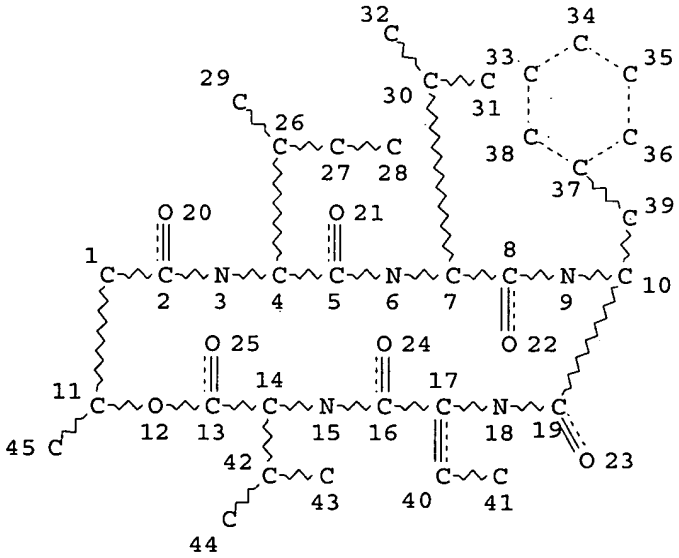

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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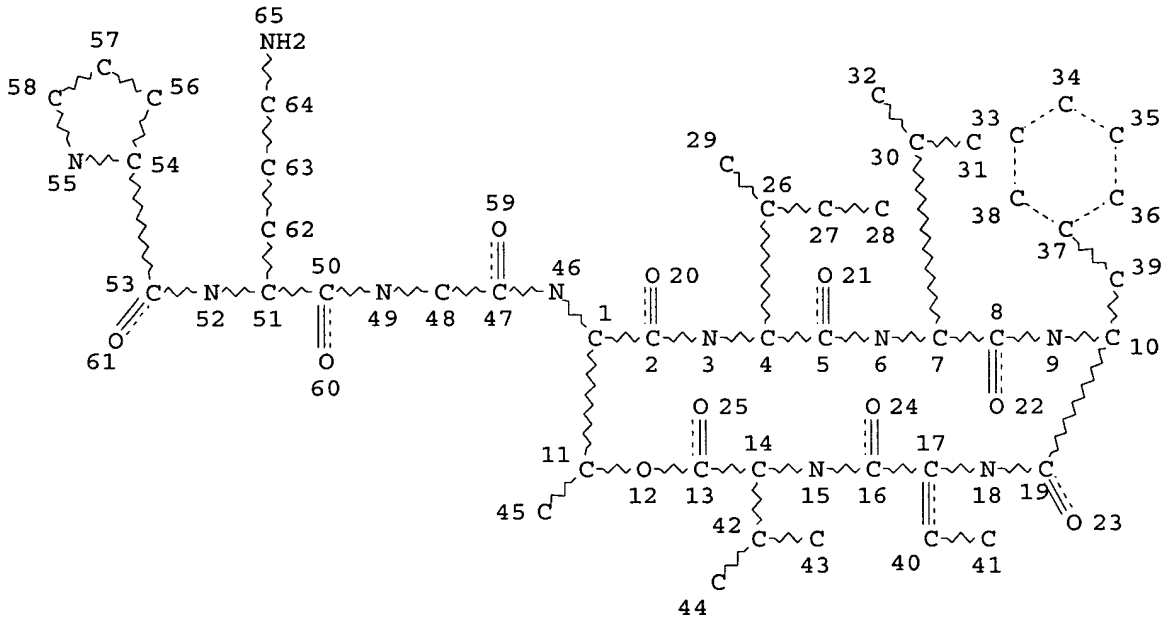

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GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 65

STEREO ATTRIBUTES: NONE
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L12 59 SEA FILE=HCAPLUS ABB=ON PLU=ON L7

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L12 ANSWER 1 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:213791 HCAPLUS
DOCUMENT NUMBER: 145:179914
TITLE: Adding pharmacogenomics to the development of new marine-derived anticancer agents
AUTHOR(S): Jimeno, Jose; Aracil, Miguel; Tercero, Juan Carlos
CORPORATE SOURCE: PharmaMar R and D, Madrid, Spain
SOURCE: Journal of Translational Medicine (2006), 4, No pp. given
CODEN: JTMOBV; ISSN: 1479-5876
URL: http://www.translational-medicine.com/content/pdf/1479-5876-4-3.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. Nature has always been a highly productive tool in the development of anticancer therapies. Renewed interest in the potential of this tool has recently been sparked by the realization that the marine ecosystem can be used for the discovery and development of new compds. with clin. potential in advanced resistant tumors. These compds. can be incorporated into combination approaches in a chronic therapy scenario. Our marine anticancer program is using the sea to develop new agents with activity in resistant solid tumors and to identify new cellular targets for therapeutic intervention. This review describes the integration of different pharmacogenomic tools in the development of Yondelis, Aplidin and Kahalalide F, three marine-derived compds. currently in Phase II or III development. Our results are reinforcing the targeted selectivity of these agents and opening the gates for customized therapies in cancer patients in the near future.

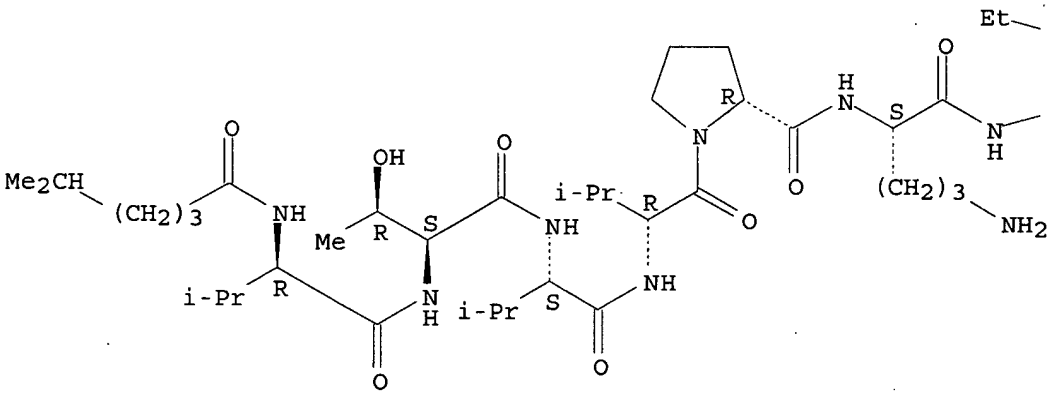
IT 149204-42-2, Kahalalide F
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(integration of different pharmacogenomic tools in development of kahalalide F may lead to development of customized, potential therapies for cancer in human)

RN 149204-42-2 HCAPLUS

CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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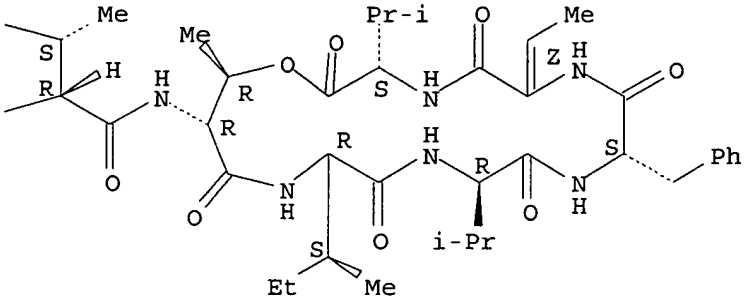


REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:100738 HCAPLUS
DOCUMENT NUMBER: 144:198849
TITLE: Novel dosage form comprising modified-release and immediate-release active ingredients
INVENTOR(S): Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar
PATENT ASSIGNEE(S): India
SOURCE: U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006024365	A1	20060202	US 2005-134633	20050519
IN 193042	A	20040626	IN 2002-MU697	20020805
US 2004096499	A1	20040520	US 2003-630446	20030729

PRIORITY APPLN. INFO.:

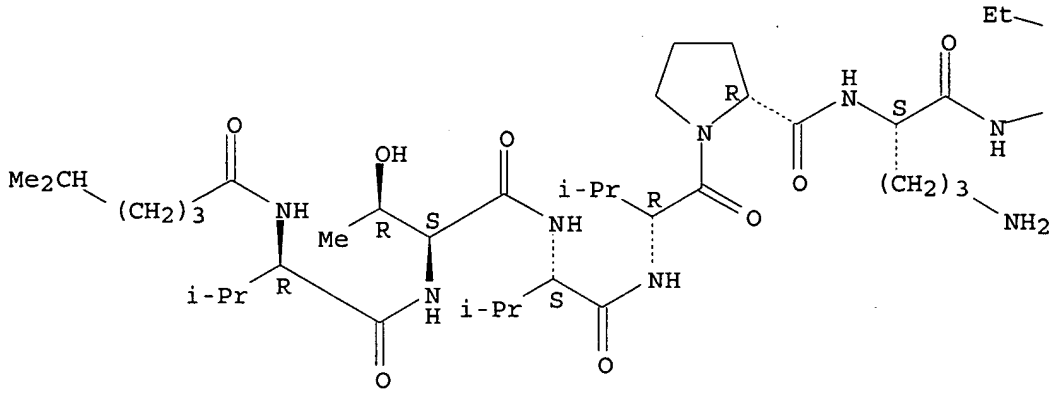
IN 2002-MU697	A	20020805
IN 2002-MU699	A	20020805
IN 2003-MU80	A	20030122
IN 2003-MU82	A	20030122
US 2003-630446	A2	20030729

AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.

IT 149204-42-2, Kahalalide F
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel dosage form comprising modified-release and immediate-release active ingredients)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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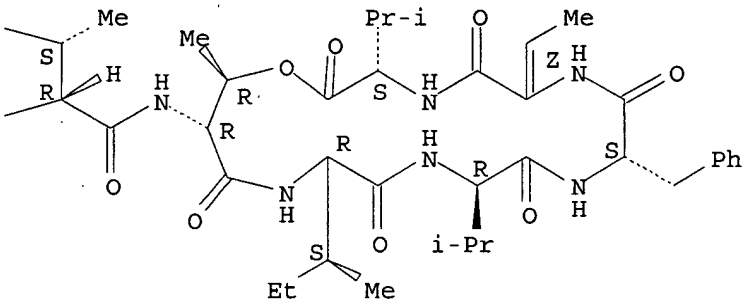


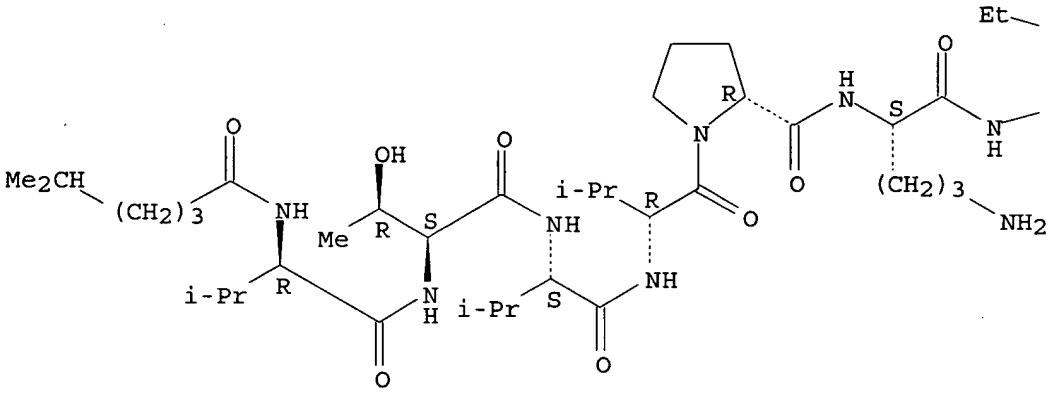
L12 ANSWER 3 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1321640 HCAPLUS
DOCUMENT NUMBER: 145:116379
TITLE: Ecteinascidin 743 (ET-743; Yondelis), aplidin, and kahalide F
AUTHOR(S): Henriquez, Ruben; Faircloth, Glynn; Cuevas, Carmen
CORPORATE SOURCE: PharmaMar, Madrid, 28770, Spain
SOURCE: Anticancer Agents from Natural Products (2005), 215-240, 2 plates. Editor(s): Cragg, Gordon M.; Kingston, David G. I.; Newman, David J. CRC Press LLC: Boca Raton, Fla.
CODEN: 69HQQY; ISBN: 0-8493-1863-7
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review on the first generation of drugs isolated from marine organisms, i.e., Ecteinascidin 743, Aplidin, and Kahalide F. Topics discussed include their origin, mechanisms of action, chemical synthesis, drug development, and clin. studies.

IT 149204-42-2, Kahalalide F
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Kahalalide F was developed to treat cancer in patient)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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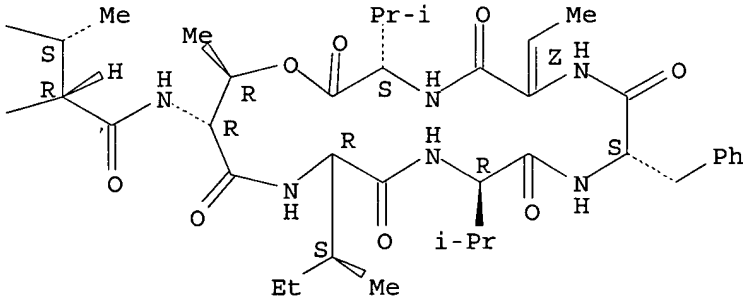


REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1290072 HCAPLUS
DOCUMENT NUMBER: 144:46998
TITLE: The X-ray crystal structure of BRCA1 tandem BRCT repeat and BACH1 phosphopeptide complex and methods and compositions for antitumor drug design
INVENTOR(S): Yaffe, Michael B.; Clapperton, Julie A.; Manke, Isaac A.; Lowery, Drew M.; Ho, Timmy; Haire, Lesley F.; Smerdon, Stephen J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 360 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2005115454	A2	20051208	WO 2005-US15981 20050509

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-569131P P 20040507

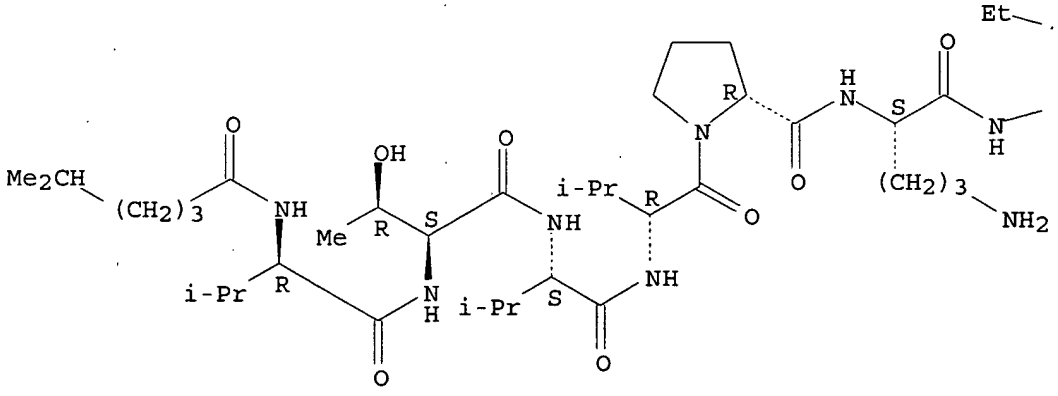
AB The present invention relates to compds. (e.g., peptidomimetics and non-peptides) that treat, prevent or stabilize cellular proliferative disorders and methods of treating, preventing, or stabilizing such disorders. The invention also provides three-dimensional structures of a BRCT domain-BACH1 phosphopeptide complex.

IT 149204-42-2, Kahalalide F
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(X-ray crystal structure of BRCA1 tandem BRCT repeat and BACH1 phosphopeptide complex and methods and compns. for antitumor drug design)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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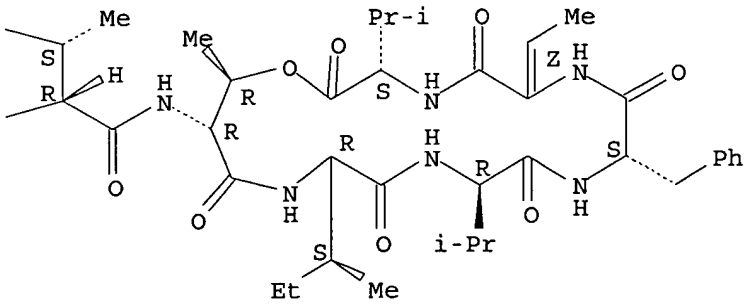


L12 ANSWER 5 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1247908 HCAPLUS
DOCUMENT NUMBER: 144:183875
TITLE: Research advances in marine antineoplastic agents
AUTHOR(S): Jiang, Qingfeng; Zhou, Youjun; Wang, Jinzheng
CORPORATE SOURCE: Department of pharmacochemistry, Second Military Medical University, Shanghai, 200433, Peop. Rep. China
SOURCE: Zhongguo Haiyang Yaowu (2004), 23(6), 58-61
CODEN: ZHYAE8; ISSN: 1002-3461
PUBLISHER: Shandongsheng Haiyang Yaowu Kexue Yanjiuso
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese

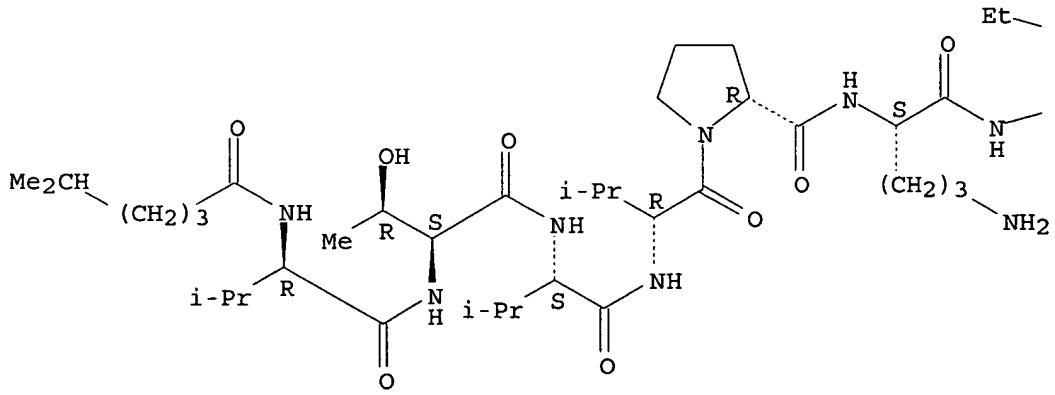
AB A review with 17 refs. on research advances in marine antineoplastic agents including: the development in the study of marine antineoplastic drugs. Owing to their unique mechanism of action, marine antineoplastic compds. have been got more and more attention and the study of marine antineoplastic drugs is becoming a focus now.

IT 149204-42-2P, Kahalalide F
RL: PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(research advances in marine antineoplastic agents)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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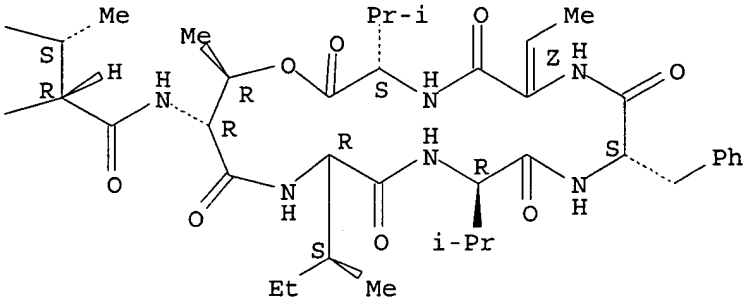

L12 ANSWER 6 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1170451 HCAPLUS
DOCUMENT NUMBER: 143:440762
TITLE: Convergent synthesis for kahalalide compounds
INVENTOR(S): Tubby, David George; Francesch Solloso, Andres; Lopez Macia, Angel; Cuevas Marchante, Carmen; Albericio Palomera, Fernando; Acosta Crespo, Gerardo; Cruz Ricondo, Luis Javier; Giralt Lledo, Ernest; Gracia Cantador, Carolina; Isidro Lobet, Albert
PATENT ASSIGNEE(S): Pharma Mar, S.A.U., Spain
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005103072	A1	20051103	WO 2005-GB1537	20050422
WO 2005103072	C1	20060518		

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2004-8958 A 20040422

AB The invention relates to the synthesis of kahalalide F or a mimic of kahalalide F by coupling of a cyclic part with a side chain fragment. Thus, kahalalide F in which the terminal 5-methylhexanoyl (5-MeHex) group has been replaced by (4S)-MeHex was synthesized by coupling between D-Pro-9 and L-Orn-8 containing fragments.

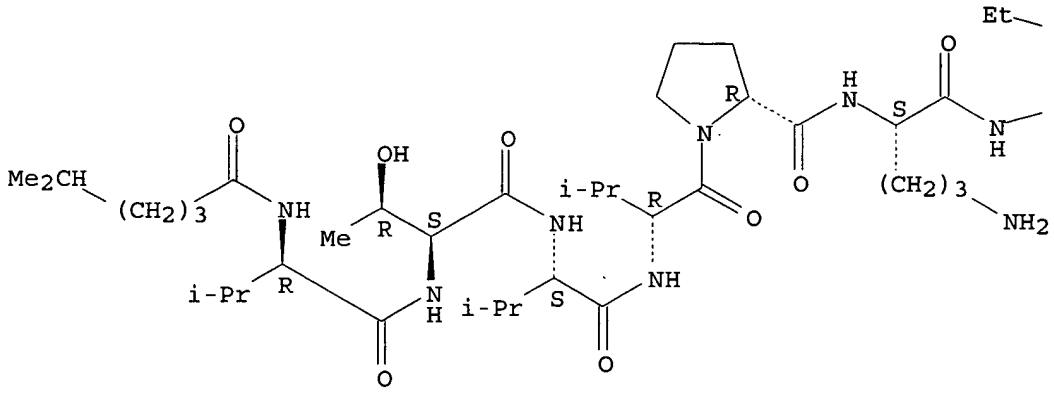
IT 149204-42-2P, Kahalalide F 681272-30-0P
868546-99-0P 868547-03-9P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(convergent synthesis for kahalalide compds.)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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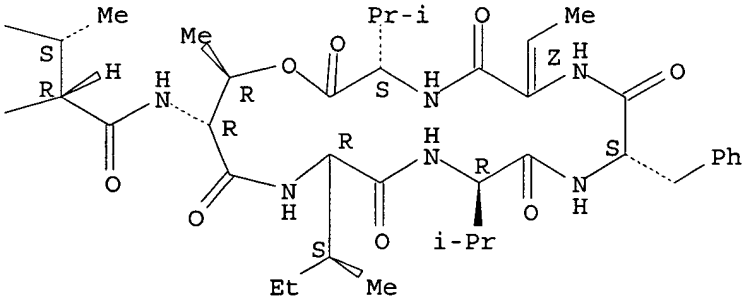
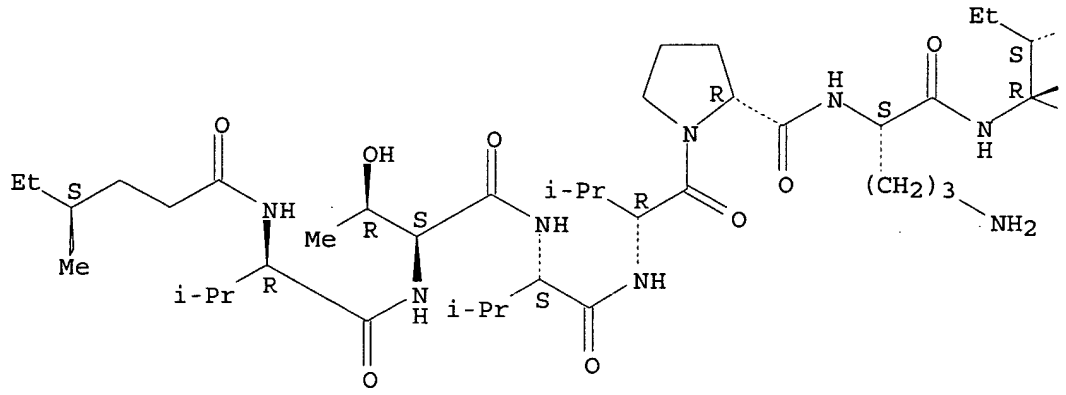


RN 681272-30-0 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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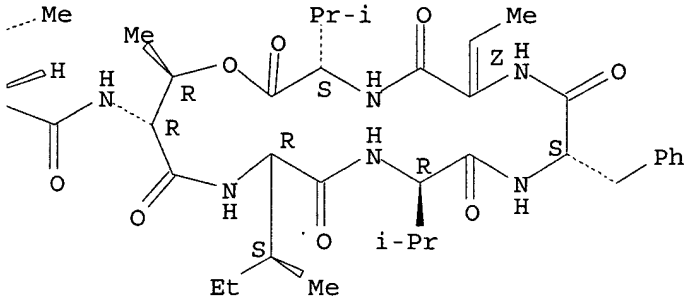
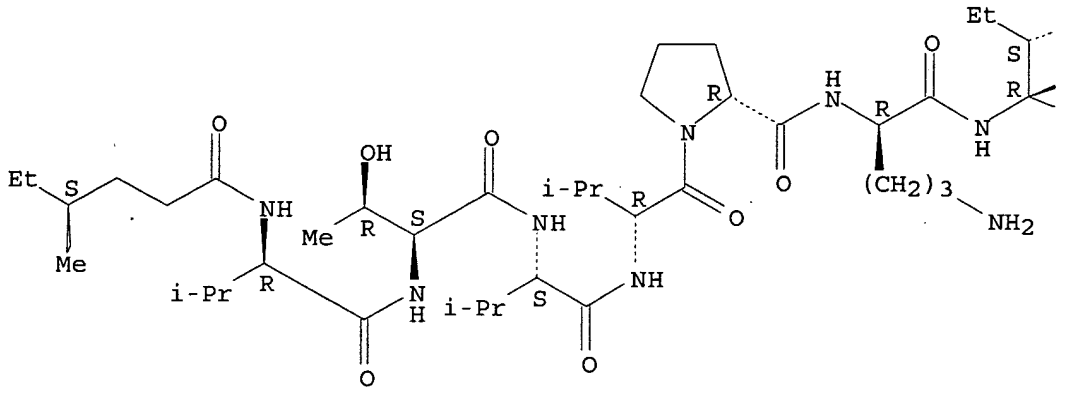


RN 868546-99-0 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-6-D-ornithine-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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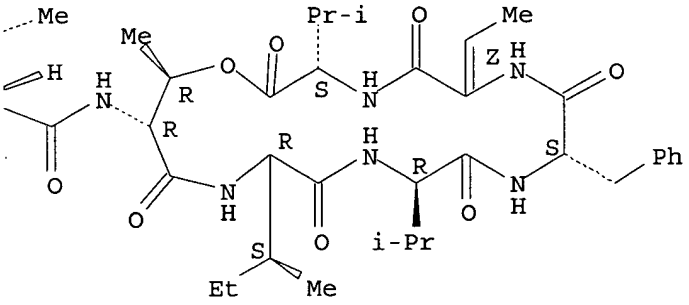
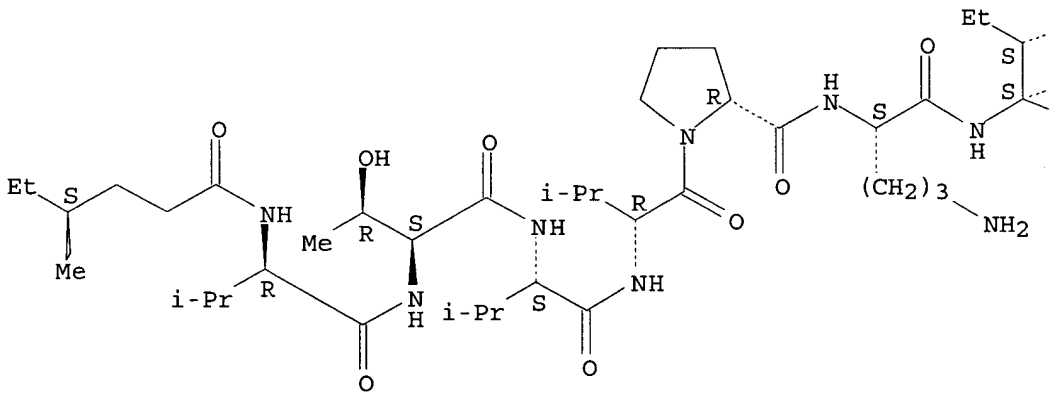


RN 868547-03-9 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-7-L-isoleucine-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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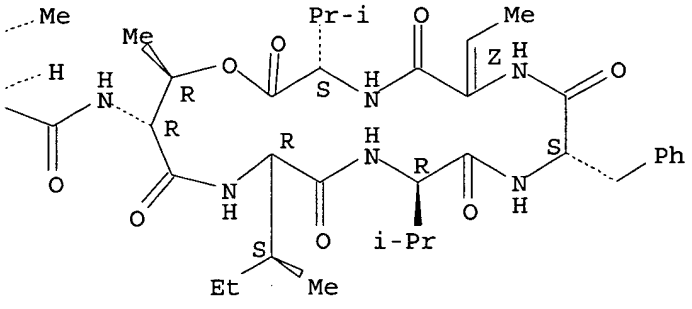


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1084693 HCAPLUS
DOCUMENT NUMBER: 144:23111
TITLE: Use of p-nitrobenzyloxycarbonyl (pNZ) as a permanent protecting group in the synthesis of kahalalide F analogs
AUTHOR(S): Lopez, Pilar E.; Isidro-Llobet, Albert; Gracia, Carolina; Cruz, Luis J.; Garcia-Granados, Andres; Parra, Andres; Alvarez, Mercedes; Albericio, Fernando
CORPORATE SOURCE: Barcelona Biomedical Research Institute, Barcelona, 08028, Spain
SOURCE: Tetrahedron Letters (2005), 46(45), 7737-7741
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

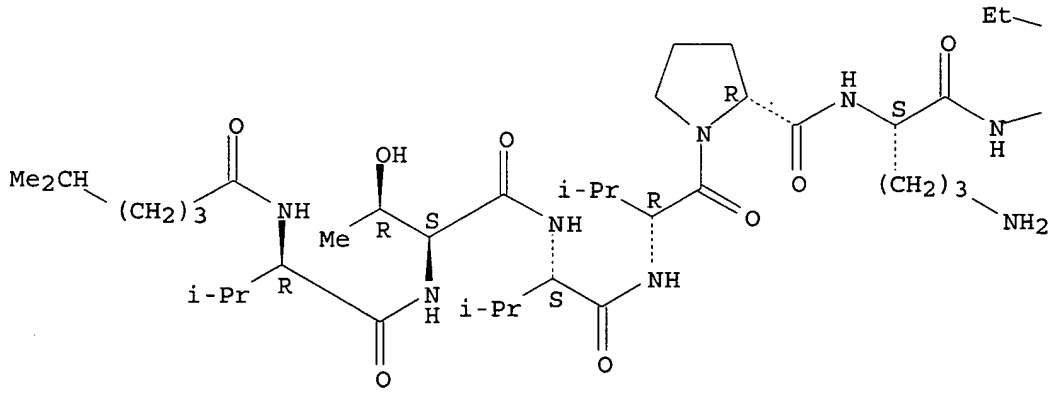
AB P-Nitrobenzyloxycarbonyl (pNZ) is used for the permanent protection of ornithine in the synthesis of derivs. of the anti-tumor cyclodepsipeptide Kahalalide F that contain acid-labile residues.

IT 149204-42-2DP, Kahalalide F, analogs 847834-59-7P
847834-61-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(p-nitrobenzyloxycarbonyl protection of ornithine residue in synthesis of kahalalide F analogs)

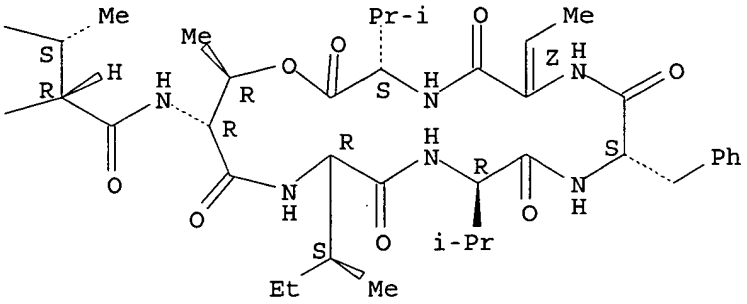
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



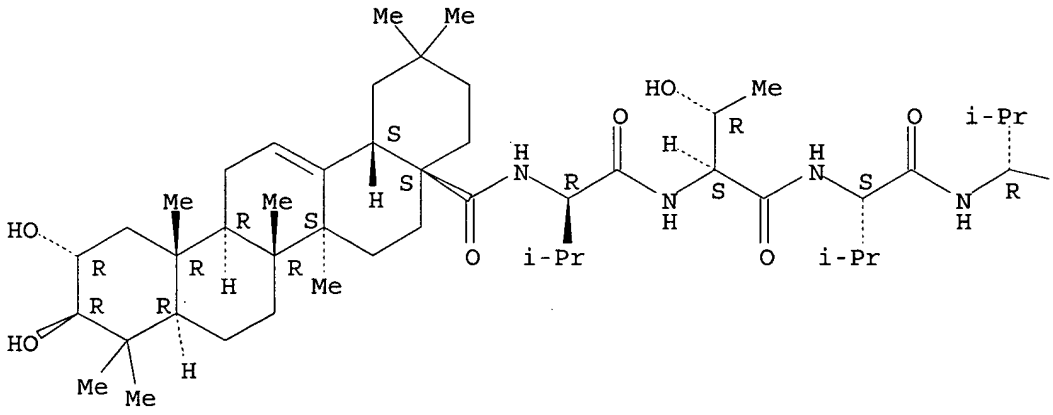
PAGE 1-B



RN 847834-59-7 HCAPLUS
CN Kahalalide F, 1-[N-[(2α,3β)-2,3-dihydroxy-28-oxoolean-12-en-28-yl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



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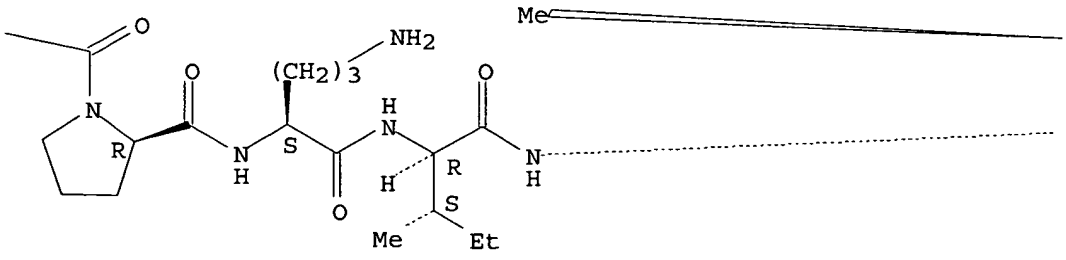

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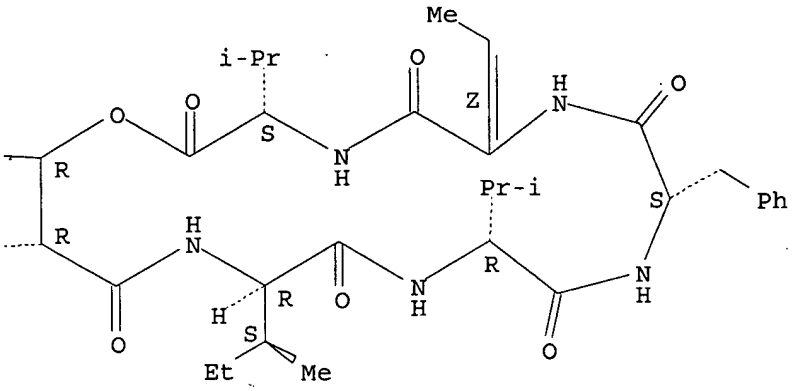
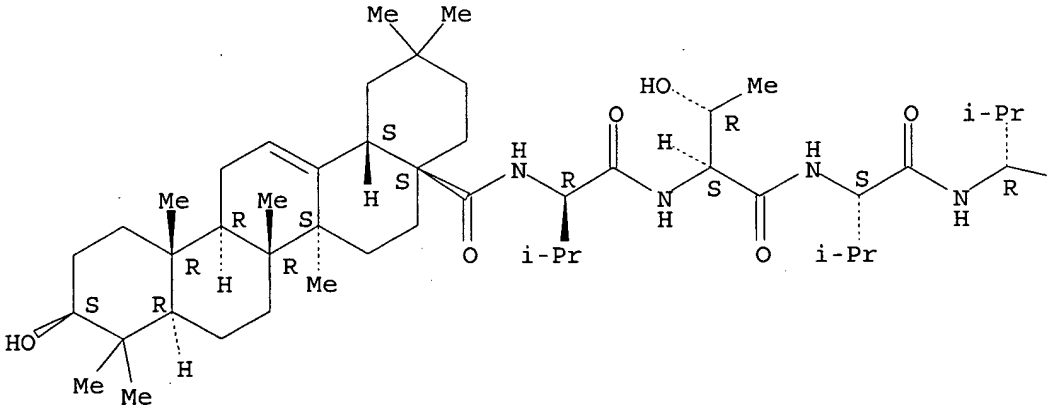


RN 847834-61-1 HCAPLUS
CN Kahalalide F, 1-[N-[(3β)-3-hydroxy-28-oxoolean-12-en-28-yl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



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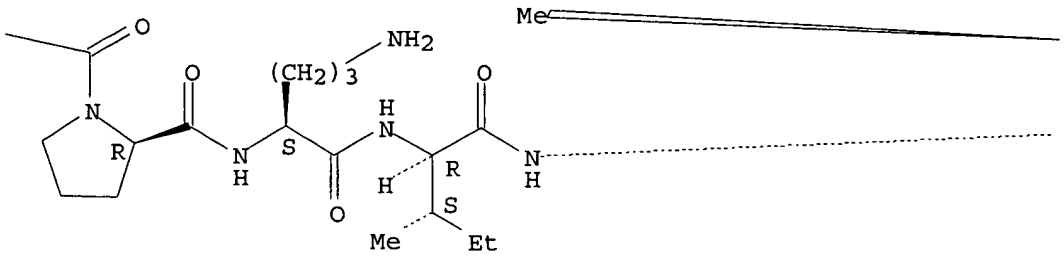

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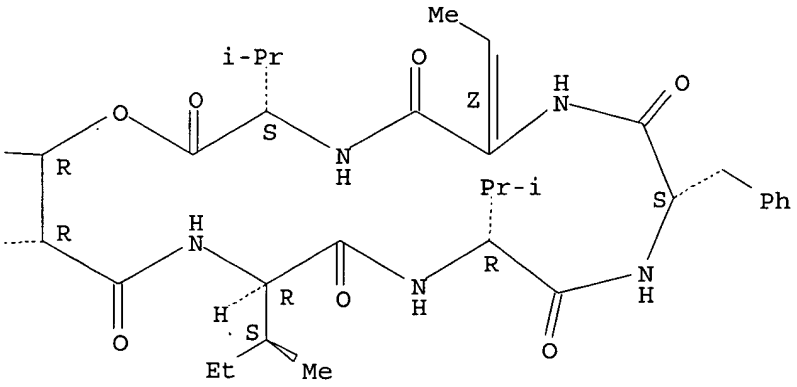


REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1004983 HCAPLUS
DOCUMENT NUMBER: 143:284098
TITLE: Genes induced by specific antitumor agents as indicators in the diagnosis, prognosis, and selection of cancer therapies
INVENTOR(S): Ross, Douglas T.; Ring, Brian Z.; Seitz, Robert S.
PATENT ASSIGNEE(S): Applied Genomics, Inc., USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2005085863 A2 20050915 WO 2005-US3943 20050204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005227266 A1 20051013 US 2005-50567 20050203
PRIORITY APPLN. INFO.: US 2004-542370P P 20040206

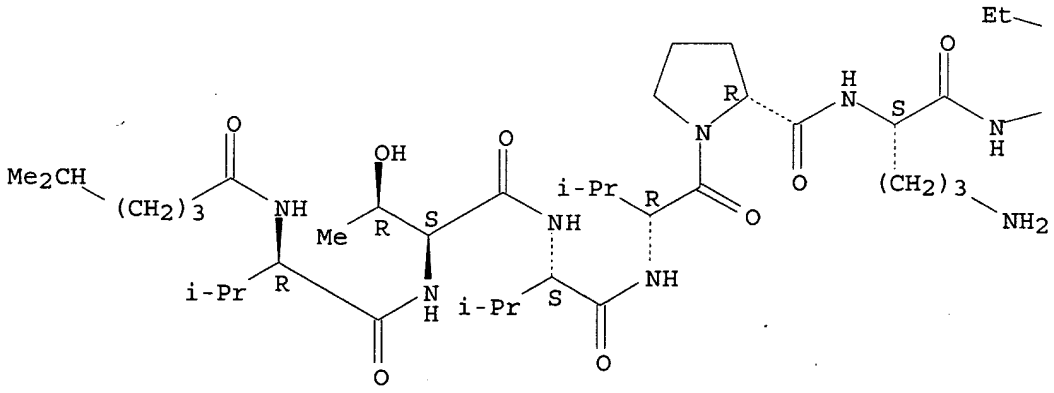
AB Genes that are induced in specific cancers in response to exposure to specific antineoplastics are identified for use in the diagnosis and prognosis of the diseases and in the selection of suitable therapies. The invention provides correlated biomarker: compound pairs, and further provides methods of using such pairs, for example, in the identification of tumors or tumor cells likely to be responsive or resistant to particular therapy, and/or the identification of chemical compds. likely (or unlikely) to be useful in the treatment of particular tumors.

IT 149204-42-2, Kahalalide F
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(genes induced by specific antitumor agents as indicators in diagnosis, prognosis, and selection of cancer therapies)

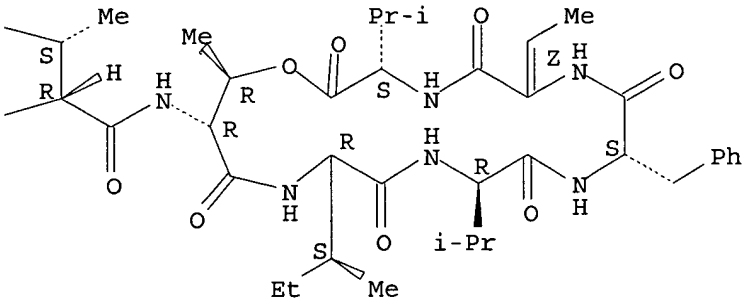
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 9 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:700422 HCAPLUS
DOCUMENT NUMBER: 143:222005
TITLE: Kahalalide F induces necrosis-like cell death that involves depletion of ErbB3 and inhibition of Akt signaling
AUTHOR(S): Janmaat, Maarten L.; Rodriguez, Jose A.; Jimeno, Jose; Kruyt, Frank A. E.; Giaccone, Giuseppe
CORPORATE SOURCE: Department of Oncology, VU University Medical Center, Amsterdam, Neth.
SOURCE: Molecular Pharmacology (2005), 68(2), 502-510
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kahalalide F (KF) is a novel marine-derived antitumor agent that is currently undergoing phase II clin. trials. The mechanism of action of KF is not well understood. In line with previous reports, we show that KF caused rapid and potent cytotoxicity in the breast cancer cell lines SKBR3 and BT474, characterized by cytoplasmic swelling and DNA clumping. Several markers of caspase-dependent apoptosis, such as phosphatidyl-serine externalization, cytochrome c release, and caspase-3 and poly(ADP-ribose) polymerase cleavage were neg. after KF exposure. Inhibitors of caspases or cathepsins failed to protect against KF cytotoxicity. Altogether, these data indicate that KF-induced cell death is a necrosis-like process. The sensitivity to KF in a panel of human tumor cell lines derived from breast (SKBR3, BT474, and MCF7), vulval (A431), non-small-cell lung (H460, A549, SW1573, and H292), and hepatic (Skhep1, HepG2, and Hep3B) carcinomas pos. correlated with ErbB3 (HER3) protein levels. A KF-resistant subline of colon carcinoma cells, HT29/KF, expressed significantly reduced levels of all ErbB receptors, but short-term KF exposure of sensitive cell lines such as SKBR3 selectively induced down-regulation of ErbB3. On the other hand, stable transfection of an ErbB3-expressing plasmid increased the KF sensitivity of H460 cells, the most resistant cell line in our panel. Finally, we found that KF efficiently inhibited the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway in sensitive cell lines and that ectopic expression of a constitutively active Akt mutant reduced KF cytotoxicity in this cell line. In summary, our results identify ErbB3 and the downstream PI3K-Akt pathway as important determinants of the cytotoxic activity of KF in vitro.

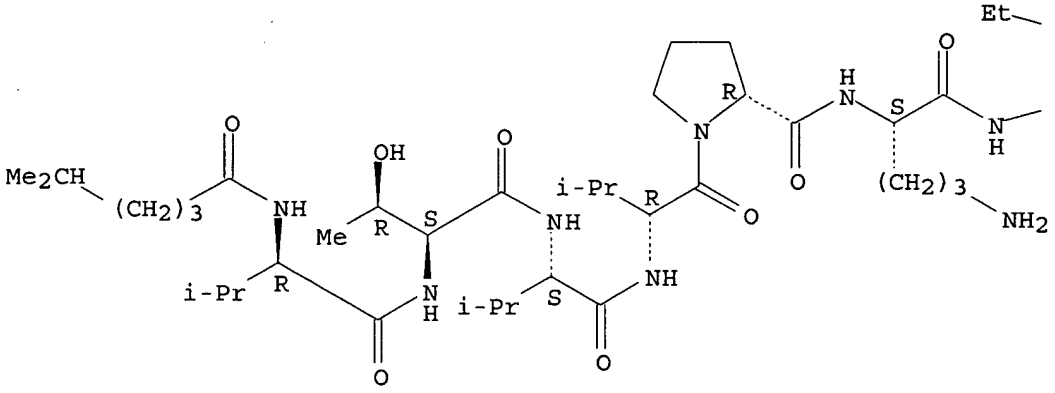
IT 149204-42-2, Kahalalide F
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(kahalalide F induces necrosis-like cell death that involves depletion of ErbB3 and inhibition of Akt signaling)

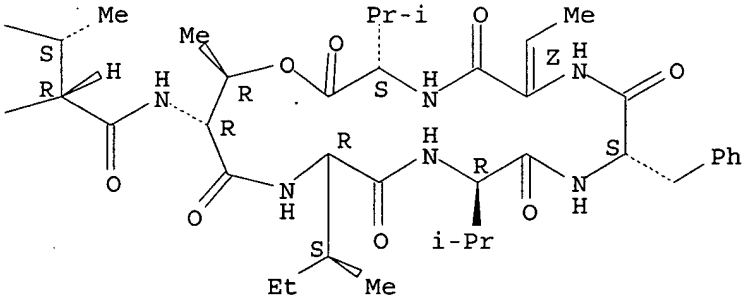
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:644590 HCAPLUS
DOCUMENT NUMBER: 143:399086
TITLE: The mechanism of action of Kahalalide F: Variable cell permeability in human hepatoma cell lines
AUTHOR(S): Sewell, J. M.; Mayer, I.; Langdon, S. P.; Smyth, J. F.; Jodrell, D. I.; Guichard, S. M.
CORPORATE SOURCE: Pharmacology and Drug Development Team, Cancer Research UK Centre, University of Edinburgh, Western General Hospital, Edinburgh, EH4 2XR, UK
SOURCE: European Journal of Cancer (2005), 41(11), 1637-1644
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Kahalalide F (KF) is a small natural peptide that showed activity in vitro and in vivo. The dose-limiting toxicity in clin. trials was transaminitis. We investigated the cytotoxicity of KF in cell lines from breast, ovary, prostate and colon cancers, but focused on hepatoma cell lines, performing mechanistic studies in HepG2 (IC50 = 0.3 μM) and PLC/PRF/5C (IC50 = 5 μM). Following KF exposure, HepG2 cells demonstrated profound ATP depletion, associated with cell swelling and cell blebbing, and increased permeability to propidium iodide (PI), annexin V (AV) and release of lactate dehydrogenase (LDH). PLC/PRF/5C cells retained their cell structure, but were permeable to PI and, following exposure to high concns. of KF, to AV. The pattern of cell permeability is similar to maitotoxin, another small cytotoxic peptide, but the differential effects on the cell membrane induced by KF in HepG2 and PLC/PRF/5C suggest specific interactions with membranes or proteins. This could lead to better drug design aimed at exploiting the potential for cell selectivity.

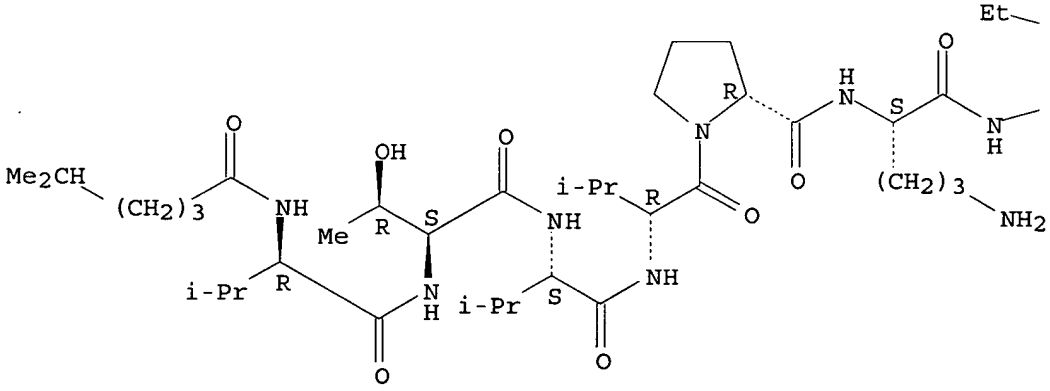
IT 149204-42-2, Kahalalide F
RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kahalalide F induced cytotoxicity in breast, prostate, ovary and colon cancer cell lines and was sensitive to HepG2 cell but resistant to PLC/PRF/5C hepatoma cell and showed cell blebbing and ATP depletion in both hepatoma cell line)

RN 149204-42-2 HCAPLUS

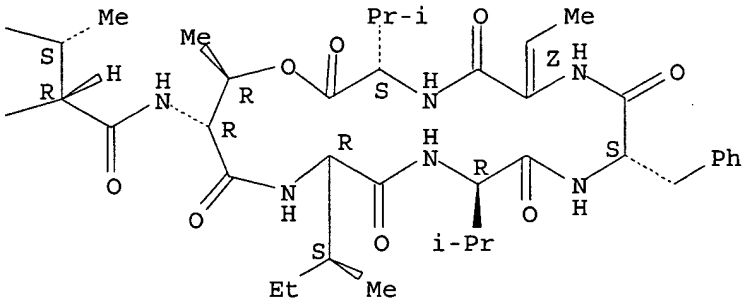
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:540495 HCAPLUS
DOCUMENT NUMBER: 143:48021
TITLE: Solvent for biogenic active pharmaceutical ingredients derived from toxins
INVENTOR(S): Weickmann, Dirk
PATENT ASSIGNEE(S): Toximed G.m.b.H., Germany
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005056027	A2	20050623	WO 2004-DE2713	20041210
WO 2005056027	A3	20050721		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10357970	A1	20050707	DE 2003-10357970	20031211
EP 1699473	A2	20060913	EP 2004-802918	20041210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				

PRIORITY APPLN. INFO.: DE 2003-10357970 A 20031211
WO 2004-DE2713 W 20041210

AB The invention relates to a solvent for biogenic active pharmaceutical ingredients, which is basically comprised of the following components: (a) 7 mL of the homeopathic substance Tarantula D4 intermingled in 15 mL of a 0.9 % NaCl solution as basic component; (b) up to 0.5 of a saturated solution of the entire poisonous cocktail from spiders of the species Loxosceles laeta, or Loxosceles gaucho, or Loxosceles Mallorca, or Loxosceles Menorca is added

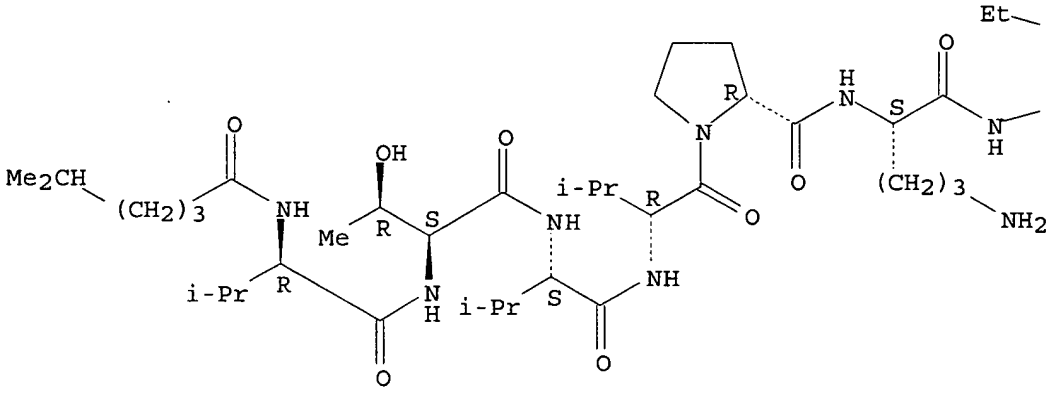
to the basic component, (c) the entire poisonous cocktail is ground into an anhydrous formic acid depending on the required quant. proportions, 1 to 2 mL of the entire exts. of poisons of bulldog ants being in turn added thereto, wherein said amount relates to a total amount of 10 mL of the entire poisonous cocktail.

IT 149204-42-2, Kahalalide F
RL: NPO (Natural product occurrence); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(solvent for biogenic active pharmaceutical ingredients derived from toxins)

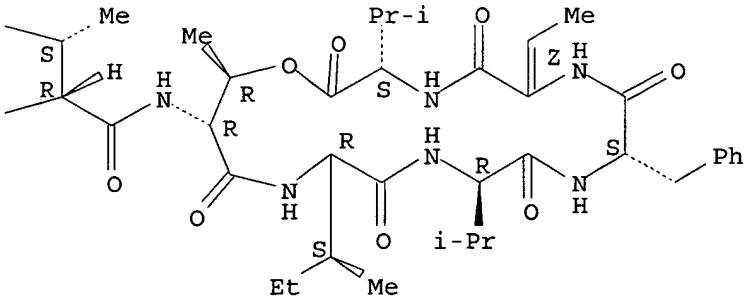
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 12 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:409661 HCAPLUS
DOCUMENT NUMBER: 142:444570
TITLE: Kahalalide-producing bacteria and methods of identifying kahalalide-producing bacteria and preparing kahalalides
INVENTOR(S): Hill, Russell T.; Hamann, Mark T.; Enticknap, Julie; Rao, Karumanchi V.
PATENT ASSIGNEE(S): University of Maryland Biotechnology Institute, USA;

University of Mississippi
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042720	A2	20050512	WO 2004-US36201	20041101
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1689848	A2	20060816	EP 2004-800512	20041101
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU				

PRIORITY APPLN. INFO.: US 2003-516006P P 20031031
WO 2004-US36201 W 20041101

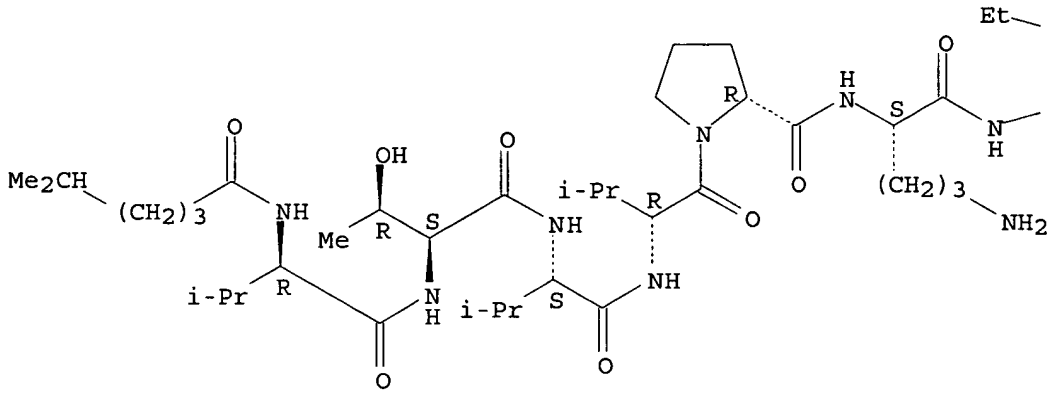
AB Disclosed are strains of Vibrio sp. bacteria that produce kahalalides or derivs. thereof, methods of isolating said strains, and 16S rRNA sequences useful in identifying kahalalides producing bacteria. Thus, based on a microbiol. examination of Bryopsis sp. and Elysia rufescens, the inventors discovered a kahalalide F-producing Vibrio associated with these organisms. It is theorized that the E. rufescens acquires kahalalide F-producing Vibrio from the surface of the Bryopsis and maintains these microbes as symbionts.

IT 149204-42-2P, Kahalalide F
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(kahalalide-producing bacteria and methods of identifying kahalalide-producing bacteria and preparing kahalalides)

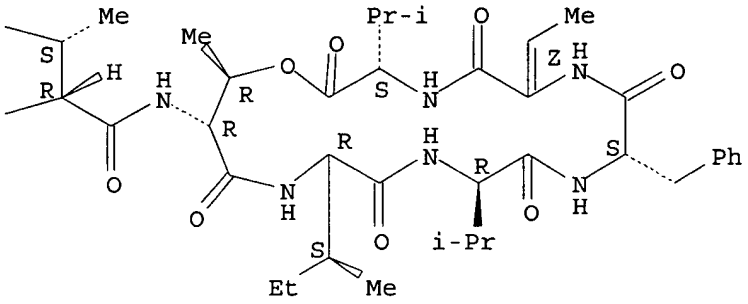
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 13 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:409543 HCAPLUS
DOCUMENT NUMBER: 142:457053
TITLE: Human protein IAP (inhibitor of apoptosis protein) nucleobase oligomers, including dsRNA, shRNA, and siRNA, and their use for enhancing apoptosis in cancer therapy
INVENTOR(S): Lacasse, Eric; McManus, Daniel
PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042558	A1	20050512	WO 2004-CA1902	20041029

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005148535	A1	20050707	US 2004-975974	20041028
CA 2542904	AA	20050512	CA 2004-2542904	20041029
EP 1682565	A1	20060726	EP 2004-789809	20041029
R: DE, FR, GB				
PRIORITY APPLN. INFO.:			US 2003-516192P	P 20031030
			WO 2004-CA1902	W 20041029

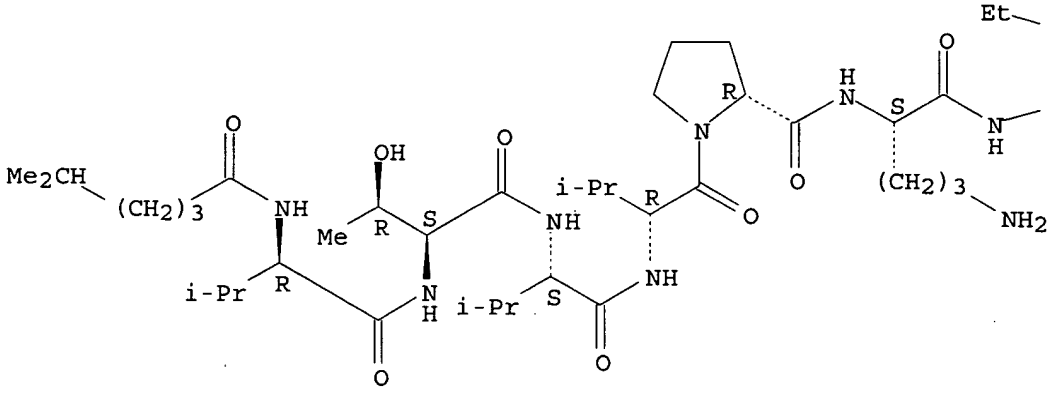
AB The invention provides nucleobase oligomers and oligonucleotide duplexes that inhibit expression of an IAP (inhibitor of apoptosis protein), and methods for using them to induce apoptosis in a cell. Specifically, the invention provides nucleic acid sequences for siRNAs and shRNAs that target human XIAP, HIAP-1 or HIAP-2 genes. The nucleobase oligomers and oligomer complexes of the present invention may also be used to form pharmaceutical compns. The invention also features methods for enhancing apoptosis in a cell by administering a nucleobase oligomer or oligomer complex of the invention in combination with a chemotherapeutic or chemosensitizing agent. RNAi sequences and vectors producing shRNA (short hairpin RNA) were transfected into HeLa cells and evaluated for their effect on XIAP, cIAP-1, or cIAP-2 protein levels. XIAP protein could also be reduced by RNAi clones in transfected breast cancer cell line MDA-MB-231. In addition, cell survival was reduced in XIAP RNAi transfected breast cancer cell line after the transfected cells were treated with TRAIL (tumor necrosis factor-related apoptosis inducing ligand).

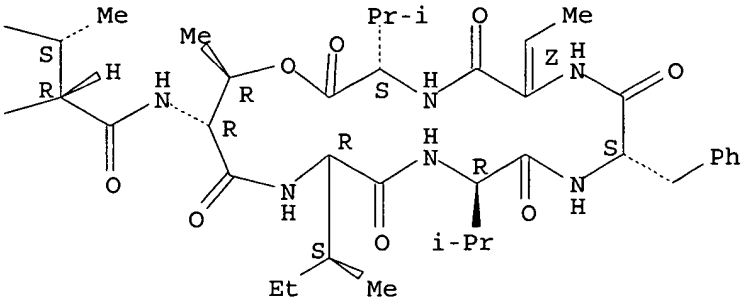
IT 149204-42-2, Kahalalide F
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human protein IAP (inhibitor of apoptosis protein) nucleobase oligomers, including dsRNA, shRNA, and siRNA, and their use for enhancing apoptosis in cancer therapy)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A





L12 ANSWER 14 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:409357 HCAPLUS
DOCUMENT NUMBER: 142:457052
TITLE: Sequences of antisense IAP (inhibitor of apoptosis protein) oligomers and their use for treatment of proliferative diseases with a chemotherapeutic agent
INVENTOR(S): Lacasse, Eric; McManus, Daniel; Durkin, Jon P.
PATENT ASSIGNEE(S): Aegera Therapeutics, Inc., Can.
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042030	A1	20050512	WO 2004-CA1900	20041029
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005119217	A1	20050602	US 2004-975790	20041028
AU 2004284855	A1	20050512	AU 2004-284855	20041029
CA 2542884	AA	20050512	CA 2004-2542884	20041029
EP 1691842	A1	20060823	EP 2004-789807	20041029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				

PRIORITY APPLN. INFO.: US 2003-516263P P 20031030
WO 2004-CA1900 W 20041029

AB The invention claims the use of an antisense oligomer to human XIAP, IAP-1 or IAP-2 genes and a chemotherapeutic agent, and compns. and kits thereof, for the treatment of proliferative diseases. The invention further claims sequences for nucleobase oligomers that are antisense IAP (inhibitor of apoptosis protein) oligomers. The antisense IAP nucleobase oligomers specifically hybridize with polynucleotides encoding an IAP and reduce the amount of an IAP protein produced in a cell. Thus by reducing the IAP

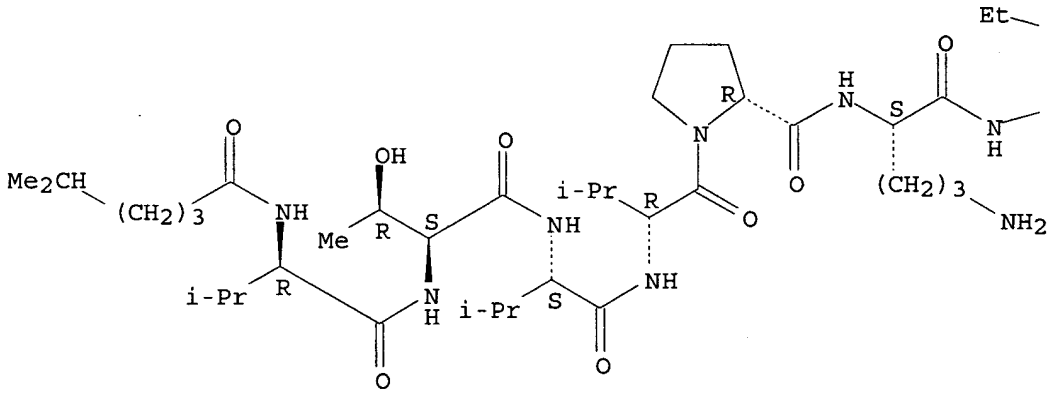
protein, the invention provides methods for inducing cancer cells to undergo apoptosis and for overriding anti-apoptotic signals in cancer cells. As an example of the invention, mice with s.c. H460 human lung carcinoma xenografts were injected intratumorally with XIAP antisense mixed-base 2'-O-Me RNA oligonucleotides (C5 and/or G4) and the drug vinorelbine. At the end of the 24 d treatment period, the mean relative tumor growth was reduced .apprx.70% in treated mice. The inhibition of tumor growth was correlated with down-regulation of human XIAP protein expression and an increased number of dead cells. The mice did not show any signs of cytotoxicity such as body weight loss.

IT 149204-42-2, Kahalalide F
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequences of antisense IAP (inhibitor of apoptosis protein) oligomers and their use for treatment of proliferative diseases with chemotherapeutic agent)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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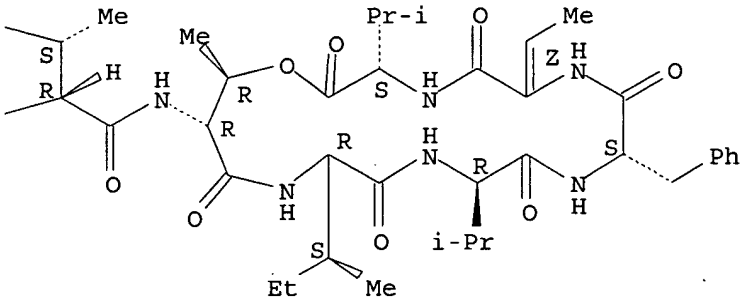


REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:283298 HCAPLUS

DOCUMENT NUMBER: 142:349042
TITLE: Combinations of chlorpromazine compounds and antiproliferative drugs for the treatment of neoplasms
INVENTOR(S): Lee, Margaret S.; Nichols, James M.; Zhang, Yanzhen; Keith, Curtis
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005027842	A2	20050331	WO 2004-US30368		20040916
WO 2005027842	A3	20051222			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2004273910	A1	20050331	AU 2004-273910		20040916
CA 2538570	AA	20050331	CA 2004-2538570		20040916
EP 1670477	A2	20060621	EP 2004-788798		20040916
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR					
NO 2006001325	A	20060606	NO 2006-1325		20060323
PRIORITY APPLN. INFO.:			US 2003-504310P	P	20030918
			WO 2004-US30368	W	20040916

OTHER SOURCE(S): MARPAT 142:349042

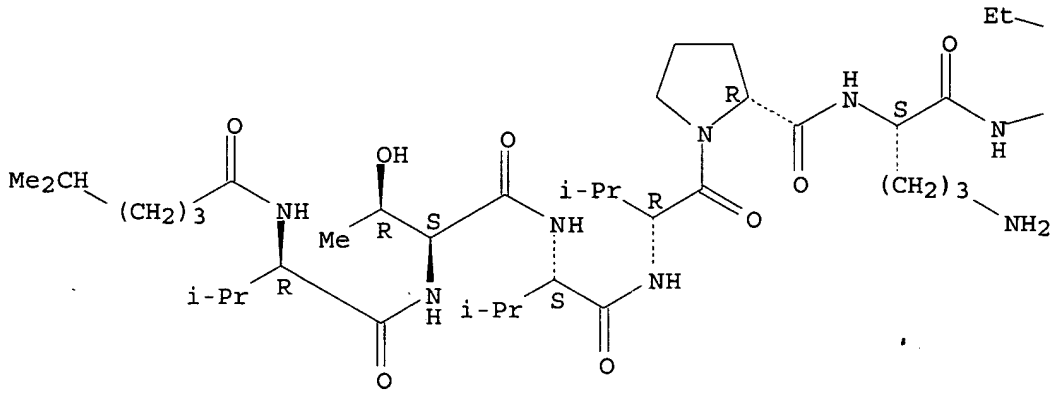
AB The invention discloses a method for treating a patient having a cancer or other neoplasm by administering chlorpromazine or a chlorpromazine analog and an antiproliferative agent simultaneously or within 14 days of each other in amts. sufficient to treat the patient.

IT 149204-42-2, Kahalalide F
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chlorpromazine compound-antiproliferative drug antitumor combination)

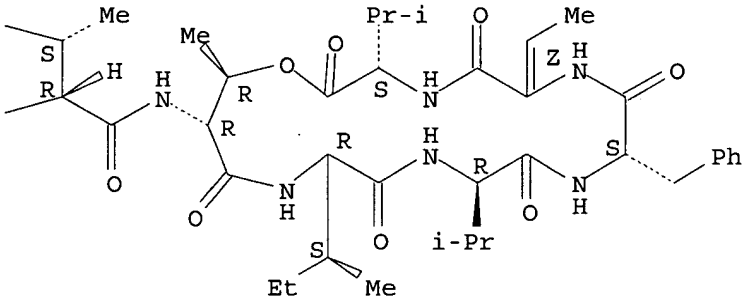
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 16 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:239012 HCAPLUS
DOCUMENT NUMBER: 142:298335
TITLE: Preparation of kahalalide F analogs as antitumor agents
INVENTOR(S): Albericio Palomera, Fernando; Fernandez Donis, Ariadna; Giralt Lledo, Ernest; Gracia Cantador, Carolina; Lopez Rodriguez, Pilar; Varon Colomer, Sonia; Cuevas Marchante, Carmen; Lopez Macia, Angel; Francesch Solloso, Andres; Jiminez Garcia, Jose-Carlos; Royo Exposito, Miriam
PATENT ASSIGNEE(S): Pharma Mar, S.A.U., Spain; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005023846	A1	20050317	WO 2004-GB3847	20040909

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

AU 2004270471	A1	20050317	AU 2004-270471	20040909
CA 2537128	AA	20050317	CA 2004-2537128	20040909
EP 1664093	A1	20060607	EP 2004-768394	20040909

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

PRIORITY APPLN. INFO.: GB 2003-21066 A 20030909
WO 2004-GB3847 W 20040909

OTHER SOURCE(S): MARPAT 142:298335

AB The invention relates to new analogs of kahalalide F in which one or more exocyclic or cyclic amino acids has been substituted by other natural or nonnatural amino acids, masked with organic groups, or been removed or in which the terminal 5-methylhexanoyl (5-MeHex) group has by substituted by other acyl groups or been removed. Thus, [(4S)-MeHex14]-kahalalide F was prepared by the solid-phase method and assayed for cytotoxic activity against various cell lines.

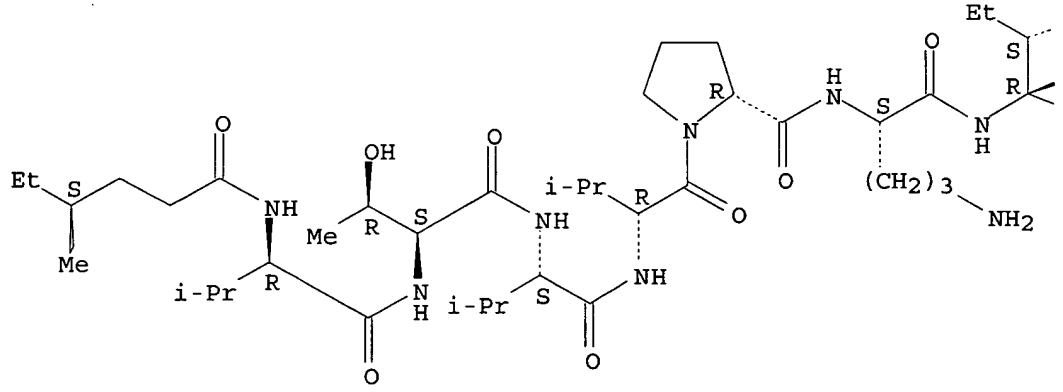
IT 681272-30-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of kahalalide F analogs as antitumor agents)

RN 681272-30-0 HCAPLUS

CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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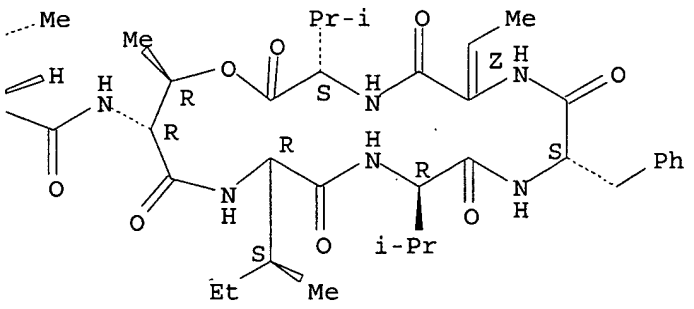

IT 149204-42-2DP, Kahalalide F, analogs 681272-31-1P
782486-09-3P 847833-53-8P 847833-57-2P
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847833-61-8P 847833-65-2P 847833-66-3P
847833-67-4P 847833-68-5P 847833-69-6P
847833-70-9P 847833-71-0P 847833-72-1P
847833-73-2P 847833-74-3P 847833-75-4P
847833-76-5P 847833-77-6P 847833-78-7P
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847834-31-5P 847834-32-6P 847834-33-7P
847834-34-8P 847834-35-9P 847834-36-0P
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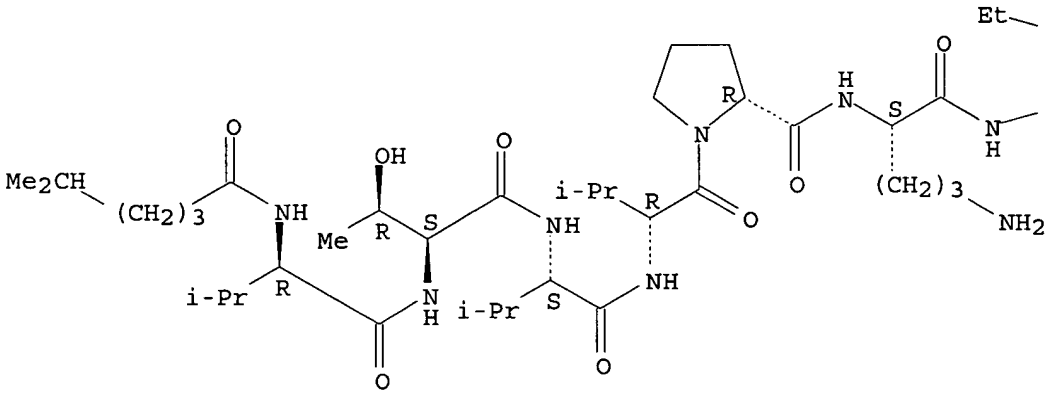
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of kahalalide F analogs as antitumor agents)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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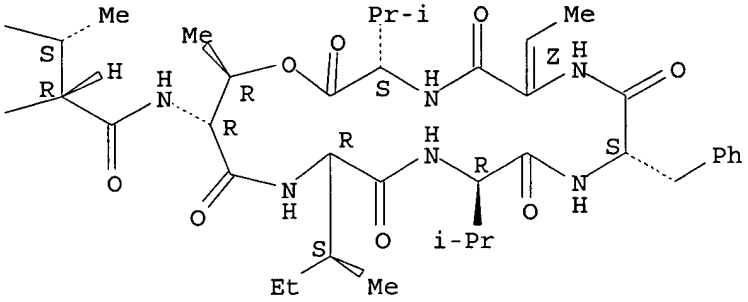
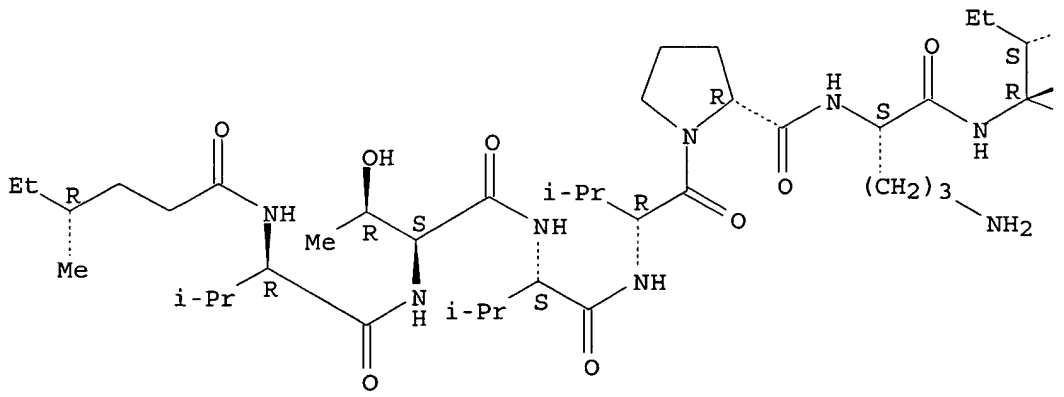


RN 681272-31-1 HCAPLUS
CN Kahalalide F, 1-[N-[(4R)-4-methyl-1-oxohexyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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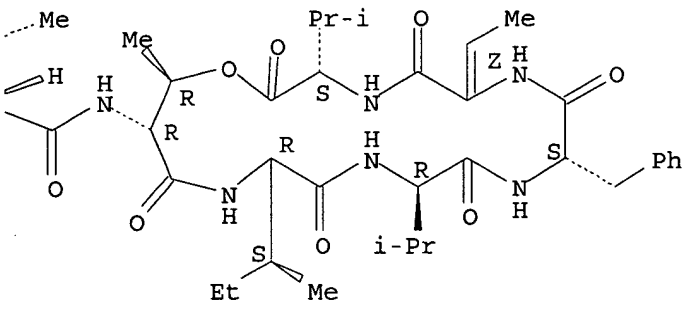
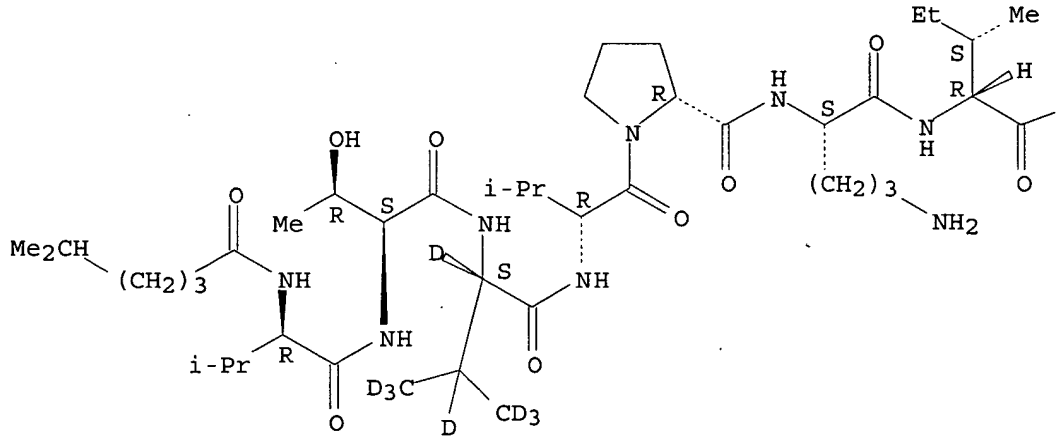


RN 782486-09-3 HCAPLUS
CN Kahalalide F, 3-(L-valine-2,3,4,4,4,4',4',4'-d8)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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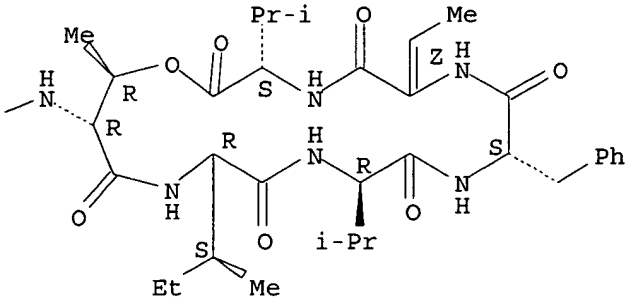
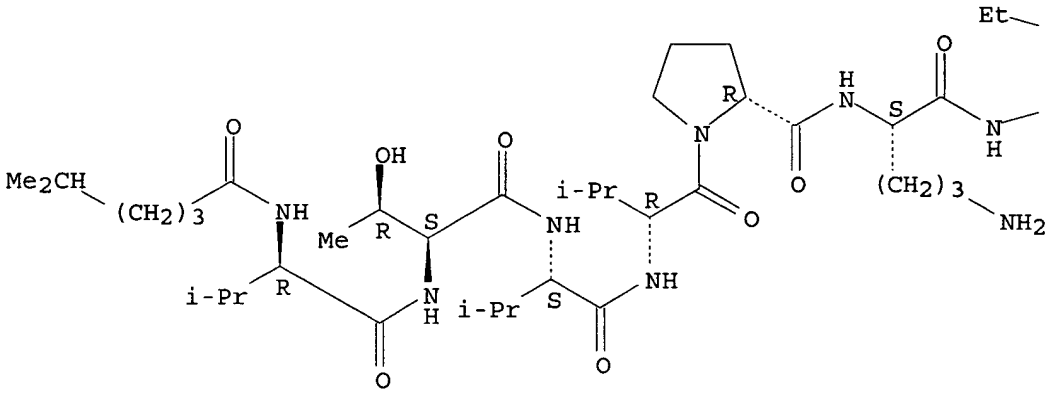


RN 847833-53-8 HCAPLUS
CN Kahalalide F, 8-D-threonine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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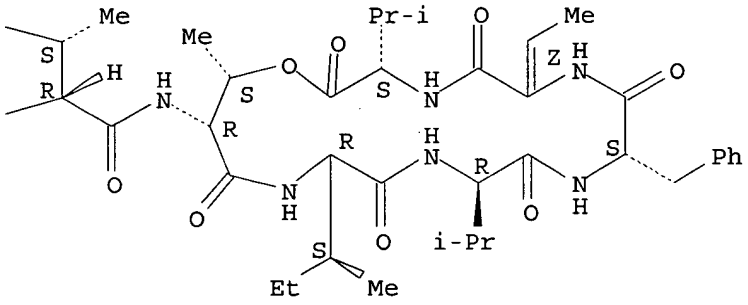
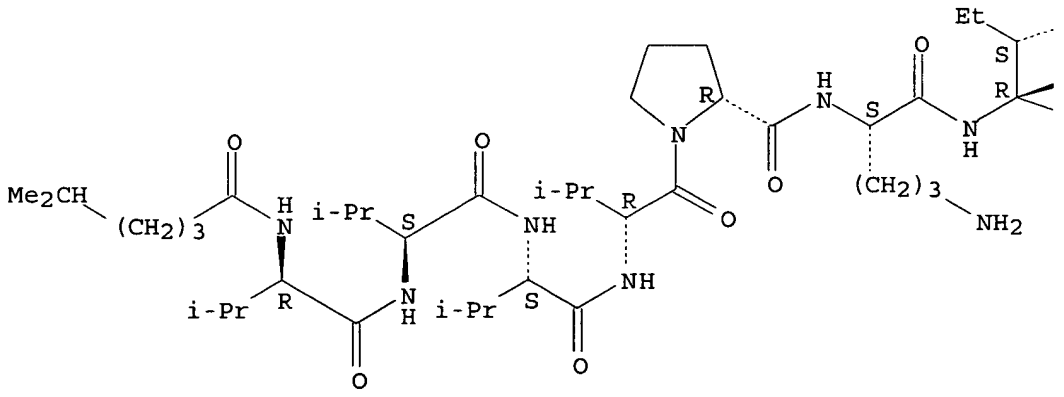


RN 847833-57-2 HCAPLUS
CN Kahalalide F, 2-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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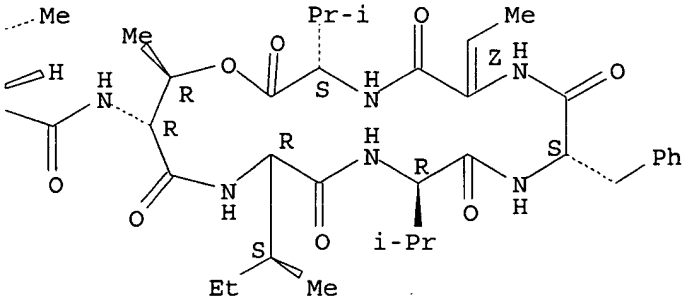
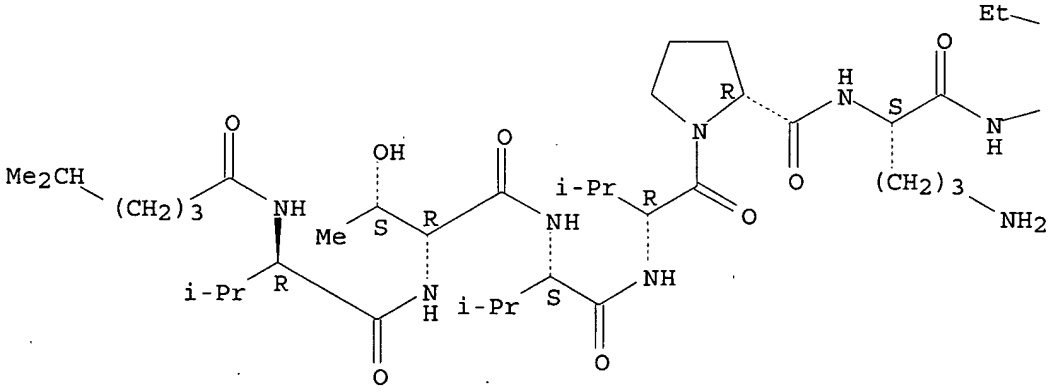


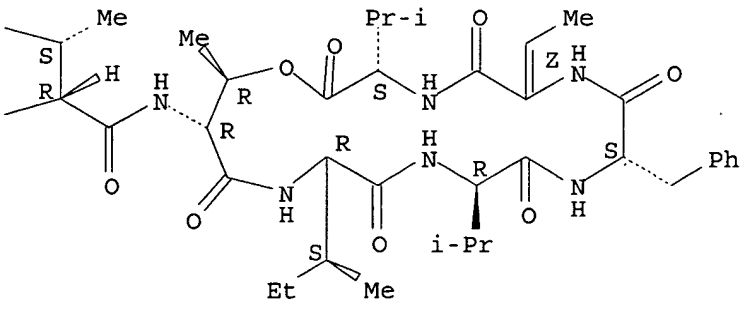
RN 847833-58-3 HCAPLUS
CN Kahalalide F, 2-D-threonine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

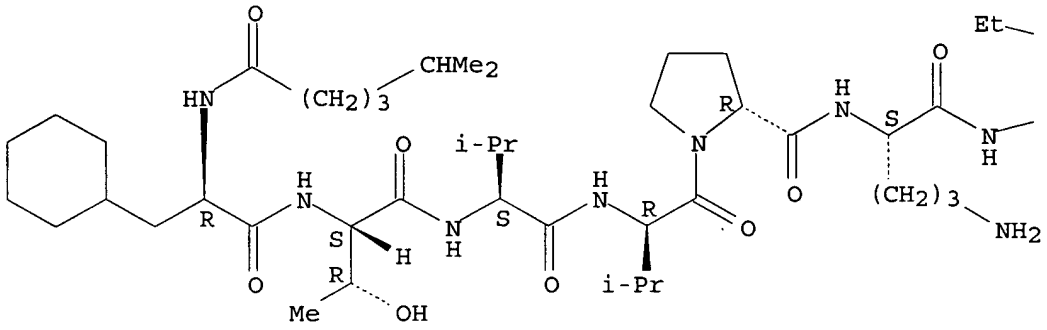


RN 847833-59-4 HCAPLUS
CN Kahalalide F, 1-[3-cyclohexyl-N-(5-methyl-1-oxohexyl)-D-alanine]- (9CI)

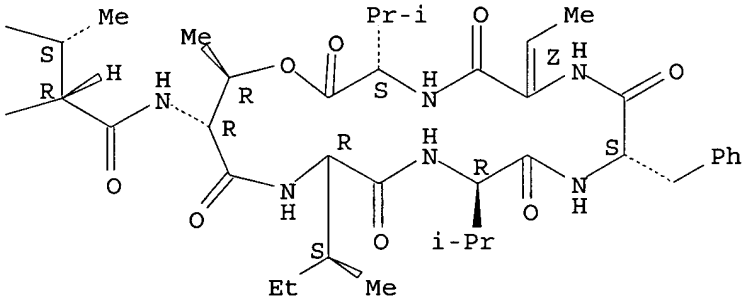
(CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



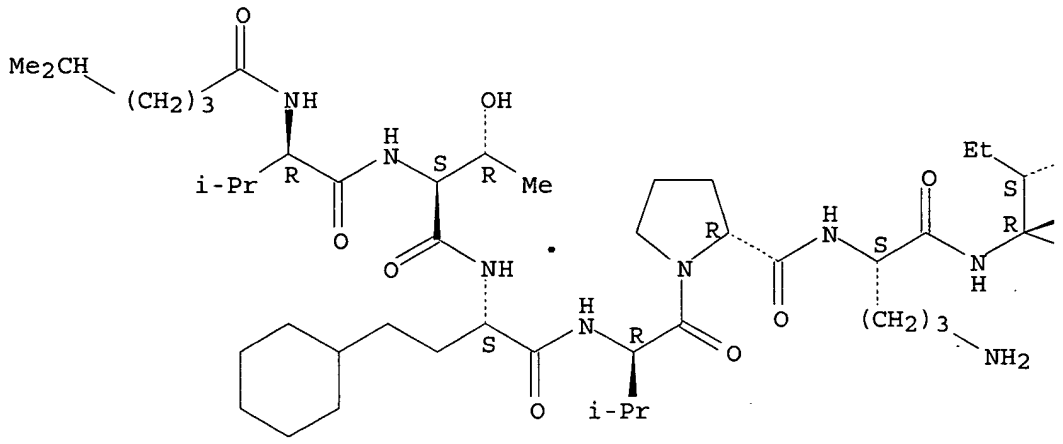
PAGE 1-B



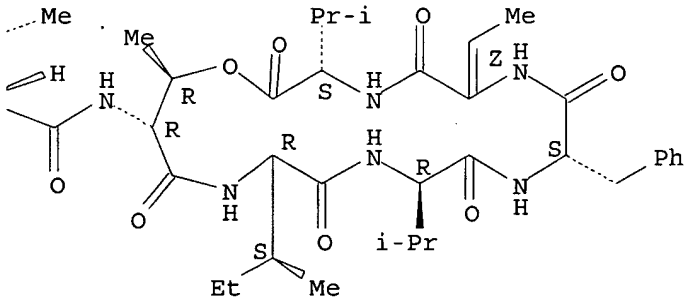
RN 847833-60-7 HCAPLUS
CN Kahalalide F, 3-[(αS)-α-aminocyclohexanebutanoic acid]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



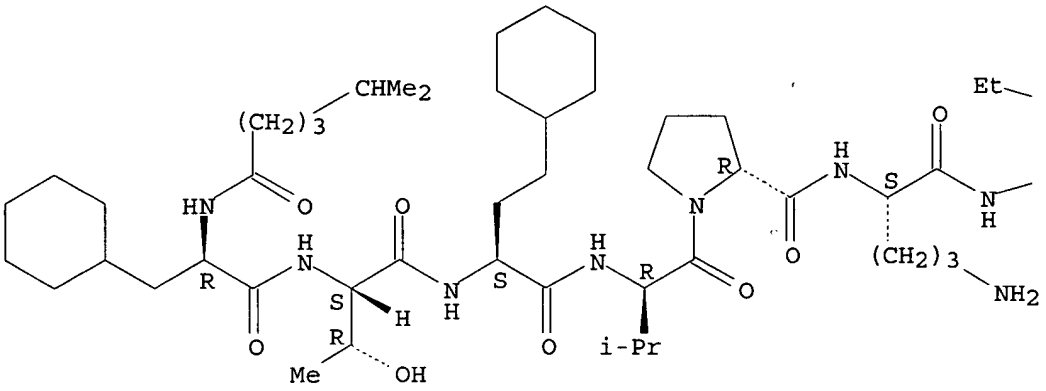
PAGE 1-B



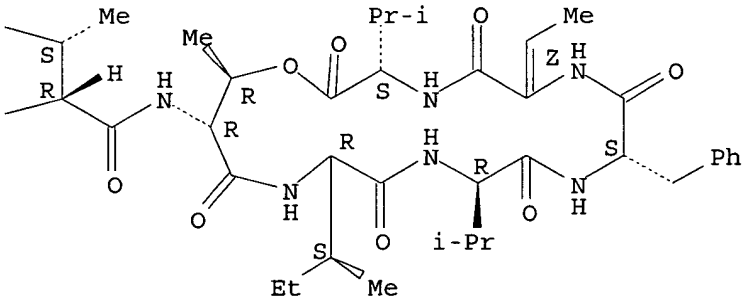
RN 847833-61-8 HCAPLUS
CN L-Valine, 3-cyclohexyl-N-(5-methyl-1-oxohexyl)-D-alanyl-L-threonyl-(αS)-α-aminocyclohexanebutanoyl-D-valyl-D-prolyl-L-ornithyl-D-alloisoleucyl-D-allothreonyl-D-alloisoleucyl-D-valyl-L-phenylalanyl-(2Z)-2-amino-2-butenoyl-, (13→8)-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



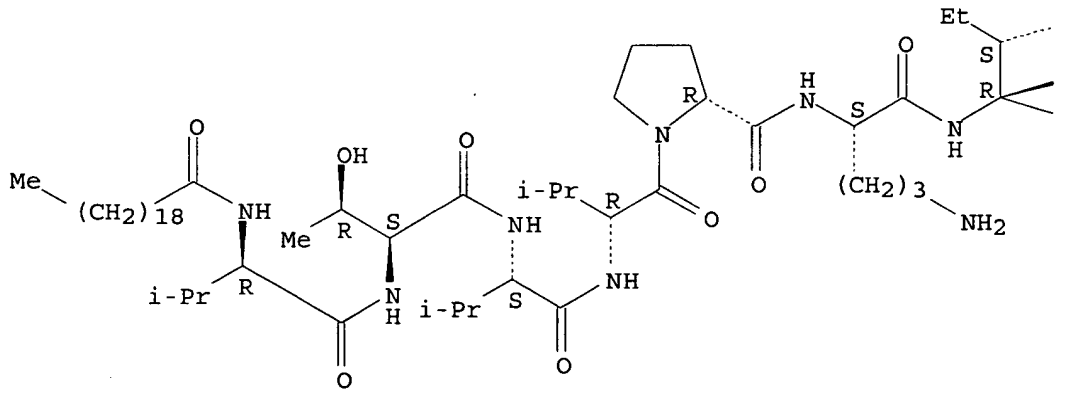
PAGE 1-B



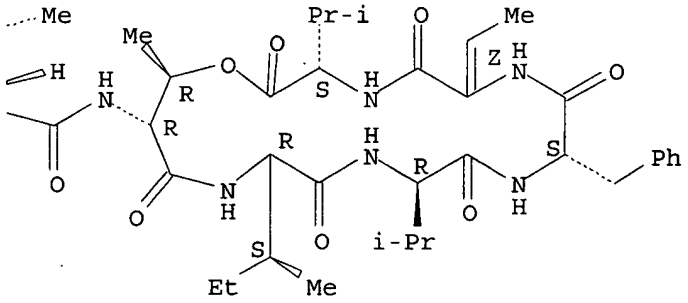
RN 847833-65-2 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxoeicosyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



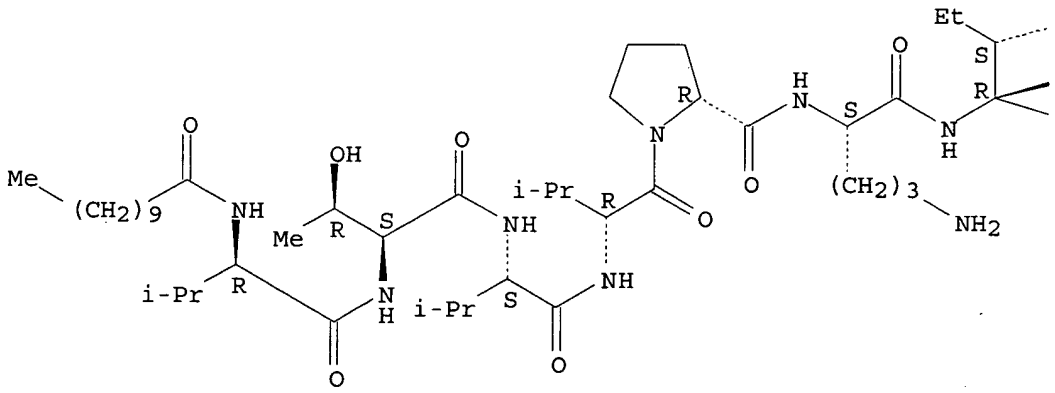
PAGE 1-B



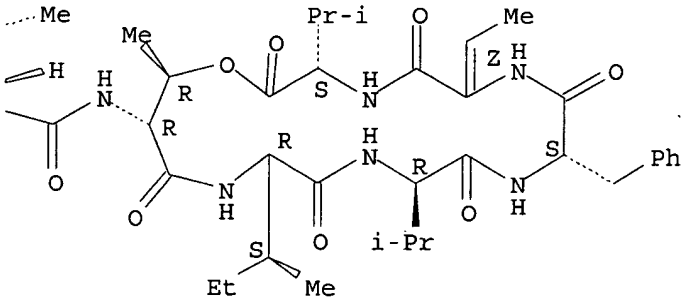
RN 847833-66-3 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxoundecyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



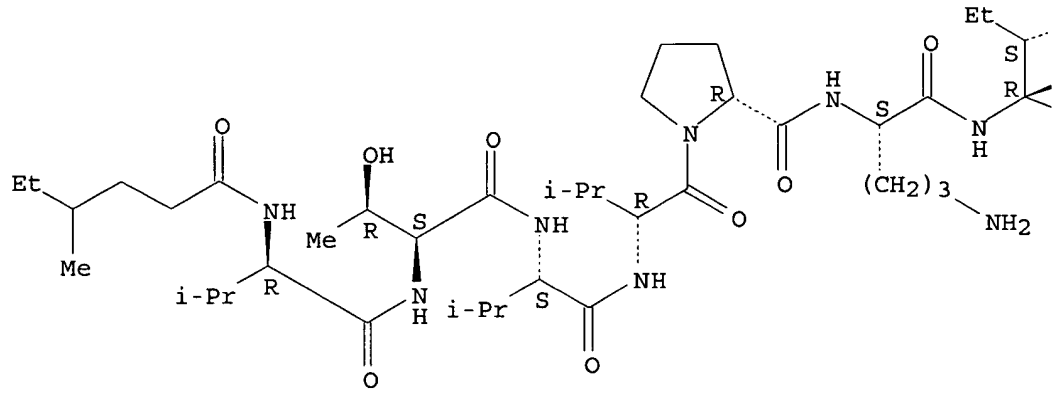
PAGE 1-B



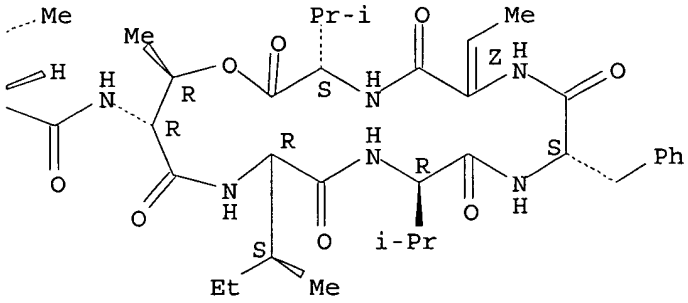
RN 847833-67-4 HCAPLUS
CN Kahalalide F, 1-[N-(4-methyl-1-oxohexyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



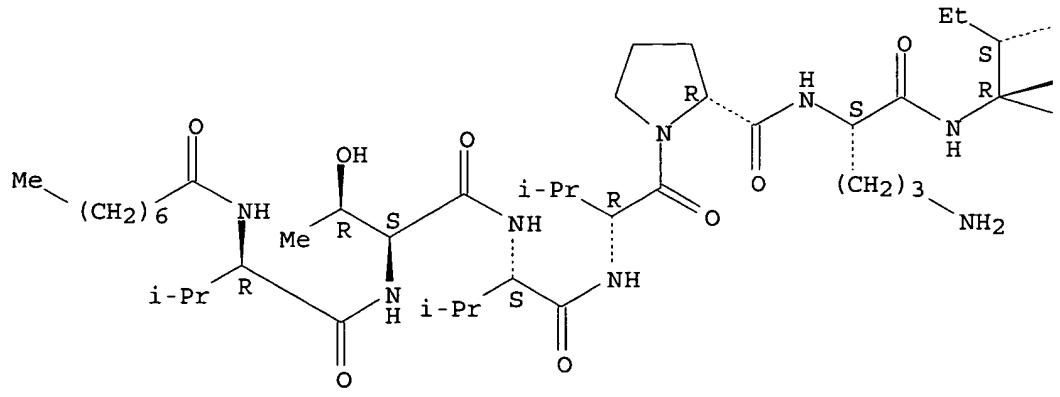
PAGE 1-B



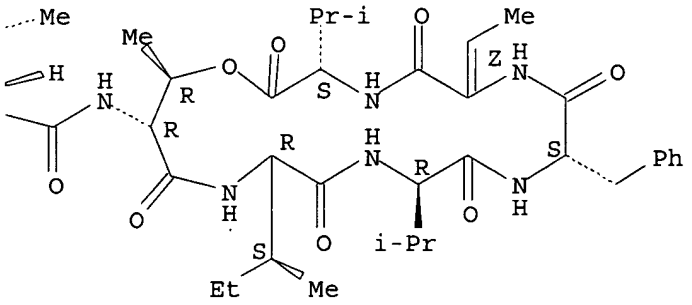
RN 847833-68-5 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxooctyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



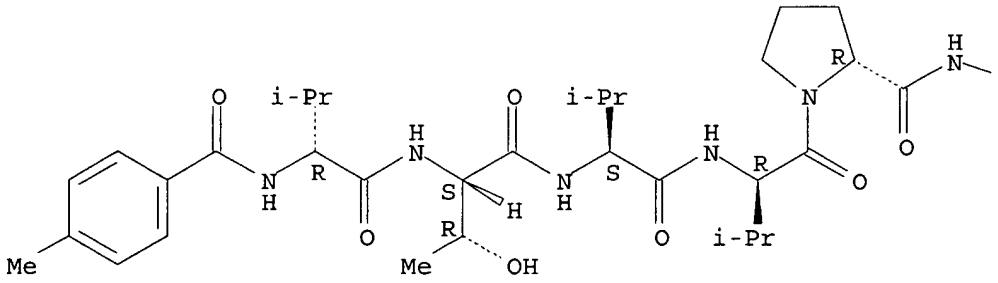
PAGE 1-B



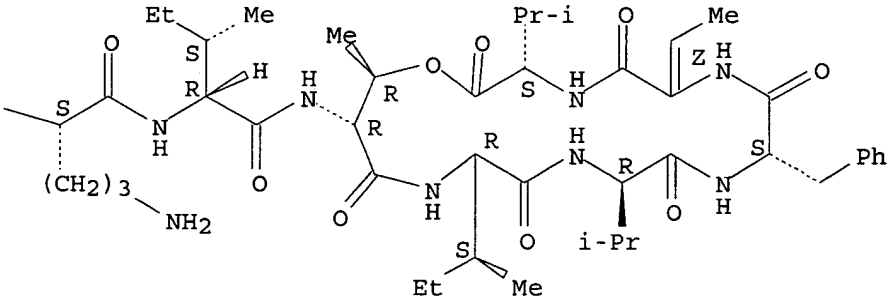
RN 847833-69-6 HCAPLUS
CN Kahalalide F, 1-[N-(4-methylbenzoyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

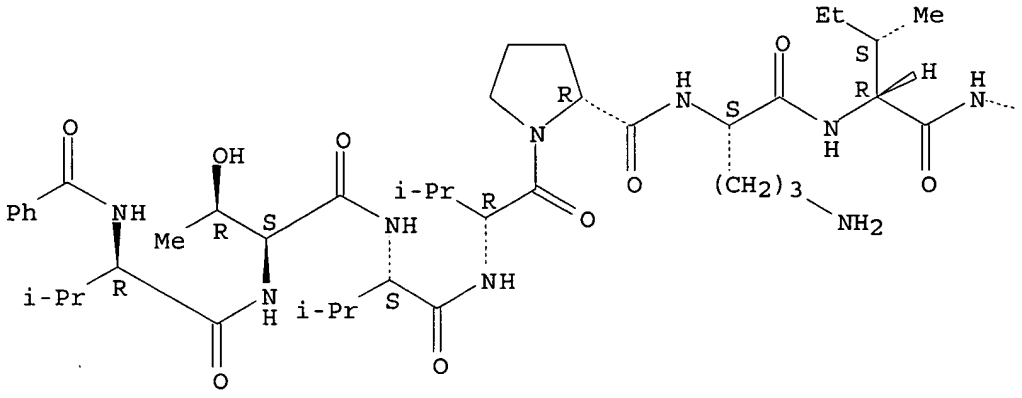


RN 847833-70-9 HCAPLUS
CN Kahalalide F, 1-(N-benzoyl-D-valine)- (9CI) (CA INDEX NAME)

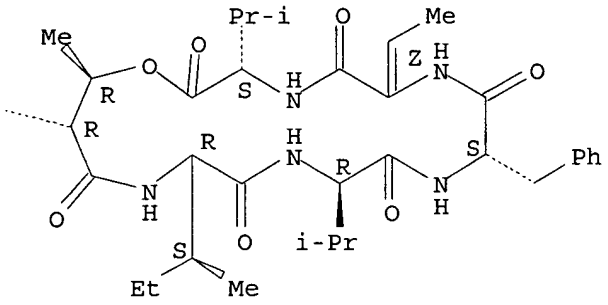
Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



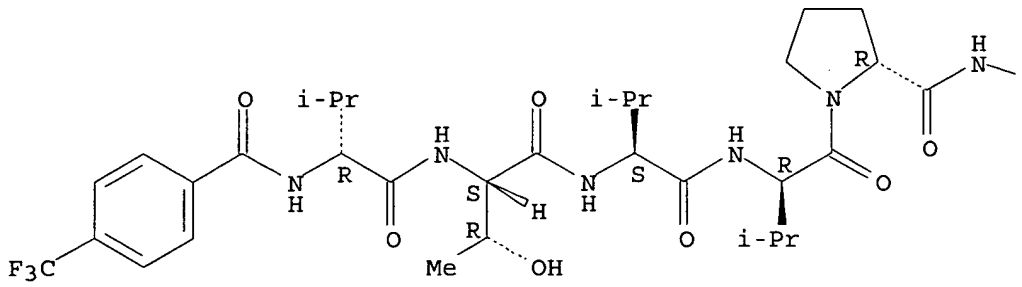
PAGE 1-B



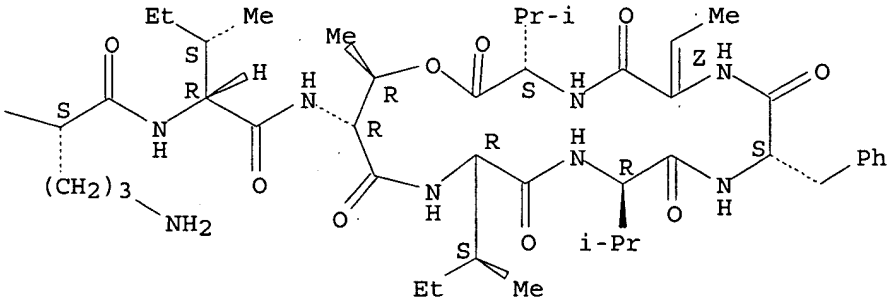
RN 847833-71-0 HCAPLUS
CN Kahalalide F, 1-[N-[4-(trifluoromethyl)benzoyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



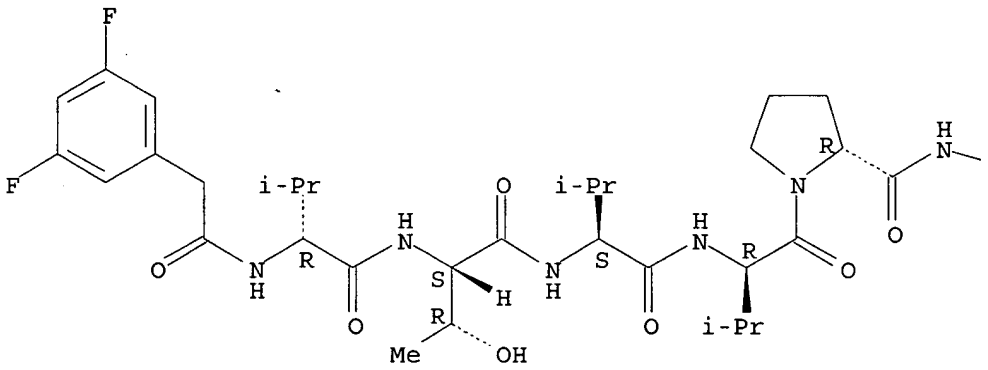
PAGE 1-B



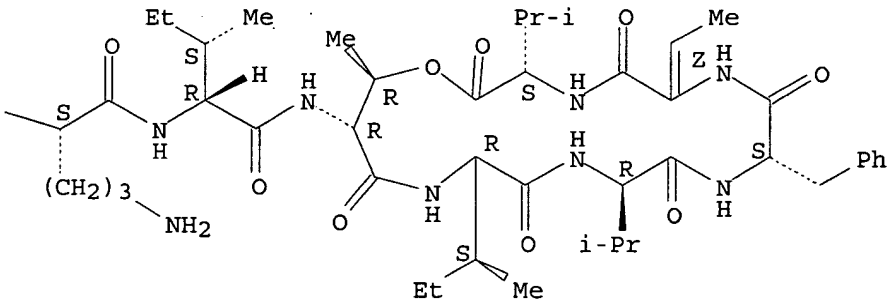
RN 847833-72-1 HCAPLUS
CN Kahalalide F, 1-[N-[(3,5-difluorophenyl)acetyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

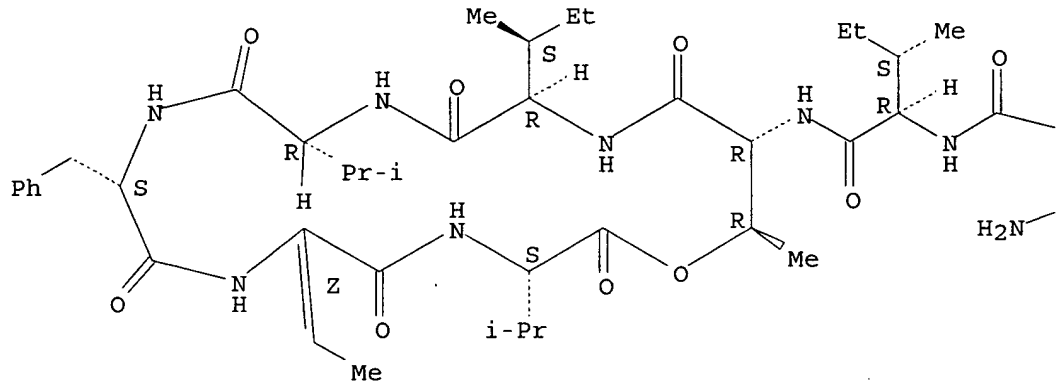


RN 847833-73-2 HCAPLUS
CN Kahalalide F, 1-[N-(1,3-benzodioxol-5-ylcarbonyl)-D-valine]- (9CI) (CA

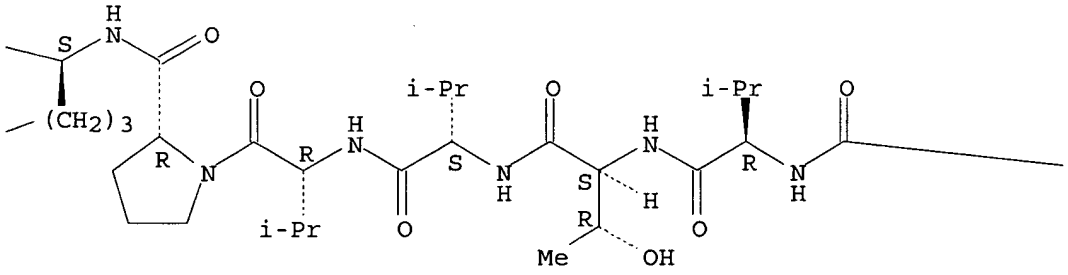
INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

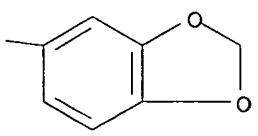
PAGE 1-A



PAGE 1-B



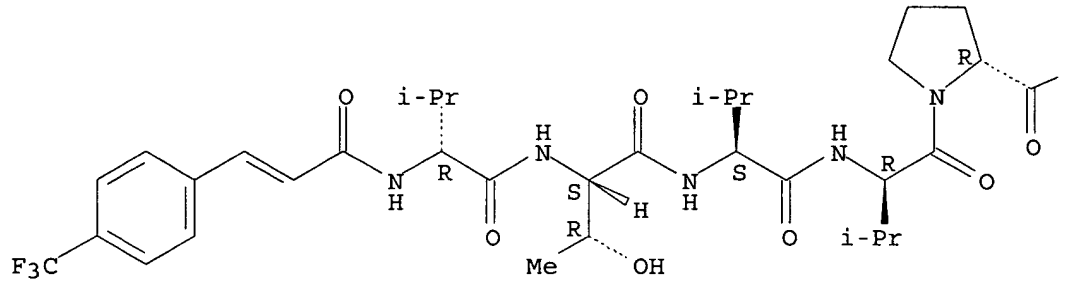
PAGE 1-C



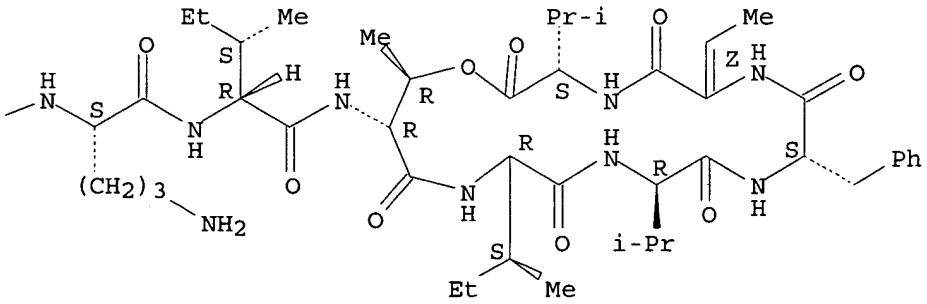
RN 847833-74-3 HCAPLUS
CN Kahalalide F, 1-[N-[1-oxo-3-[4-(trifluoromethyl)phenyl]-2-propenyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



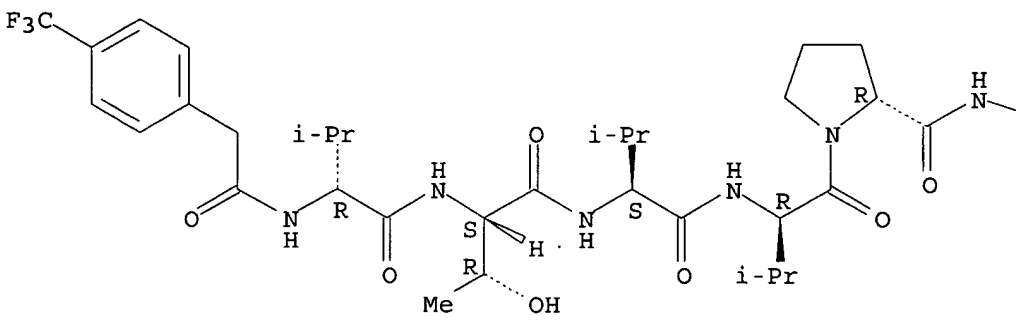
PAGE 1-B



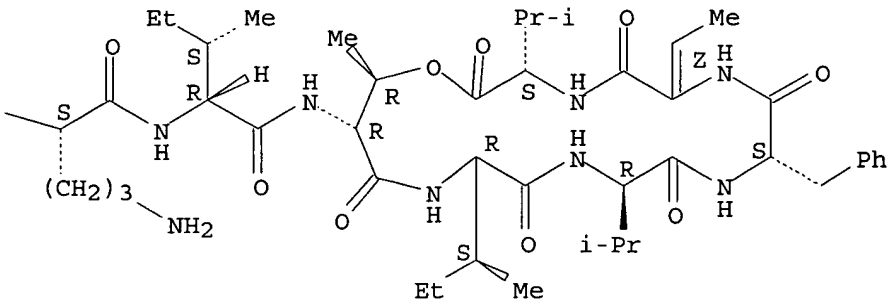
RN 847833-75-4 HCAPLUS
CN Kahalalide F, 1-[N-[[4-(trifluoromethyl)phenyl]acetyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



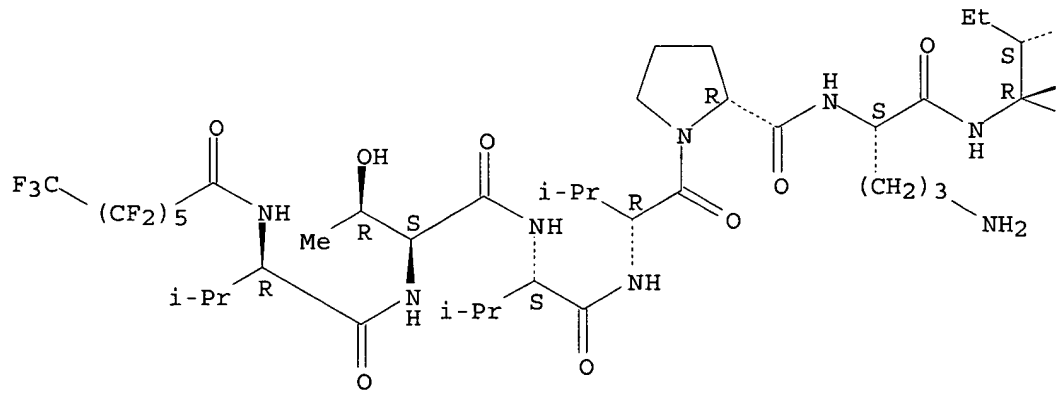
PAGE 1-B



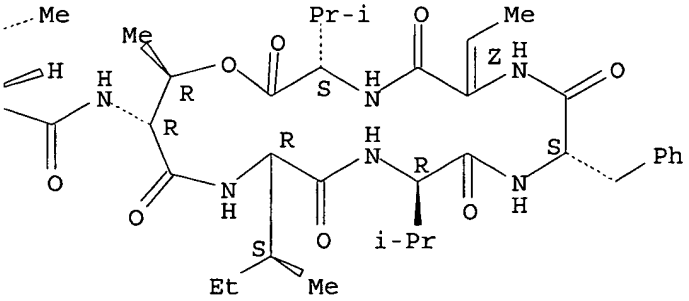
RN 847833-76-5 HCAPLUS
CN Kahalalide F, 1-[N-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-1-oxoheptyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

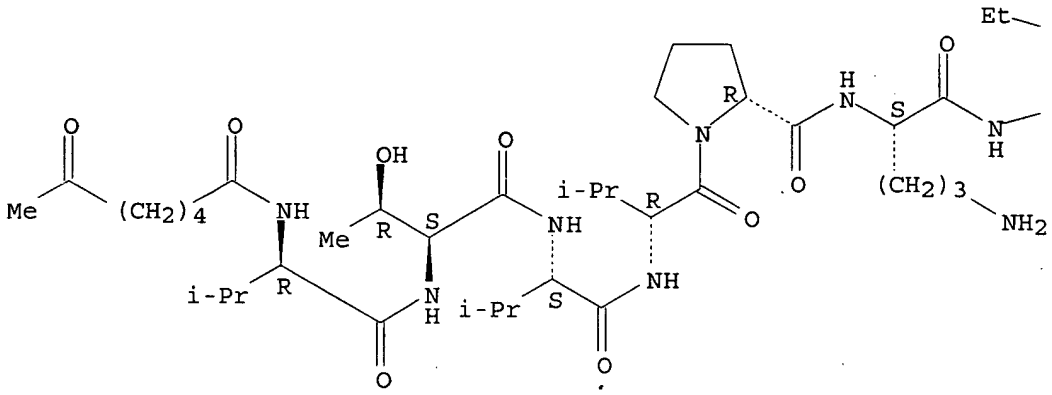


RN 847833-77-6 HCAPLUS

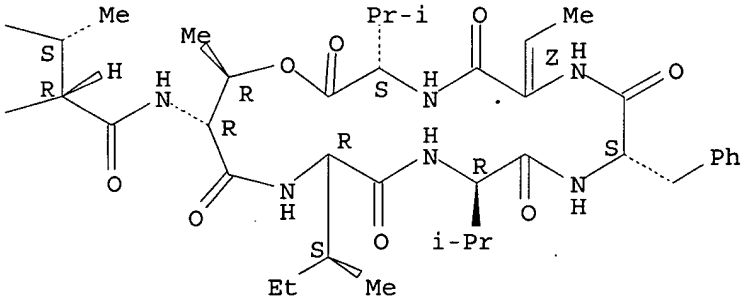
CN Kahalalide F, 1-[N-(1,6-dioxoheptyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



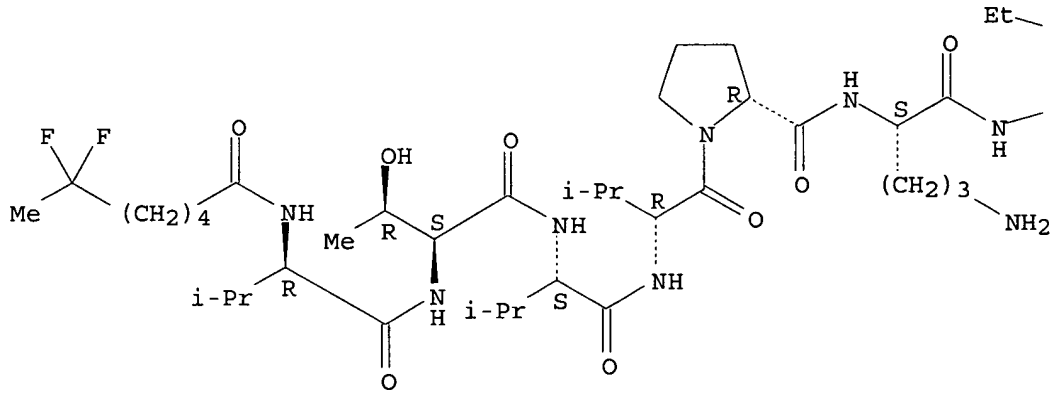
PAGE 1-B



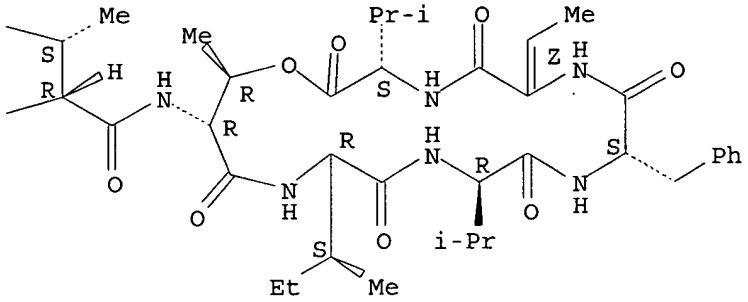
RN 847833-78-7 HCAPLUS
CN Kahalalide F, 1-[N-(6,6-difluoro-1-oxoheptyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



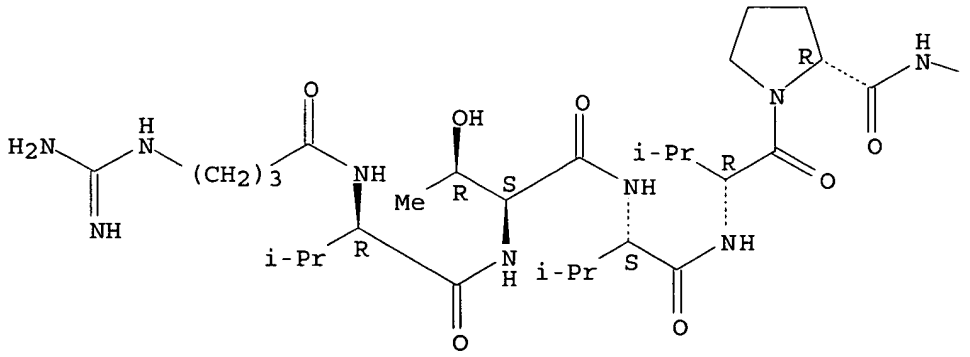
PAGE 1-B



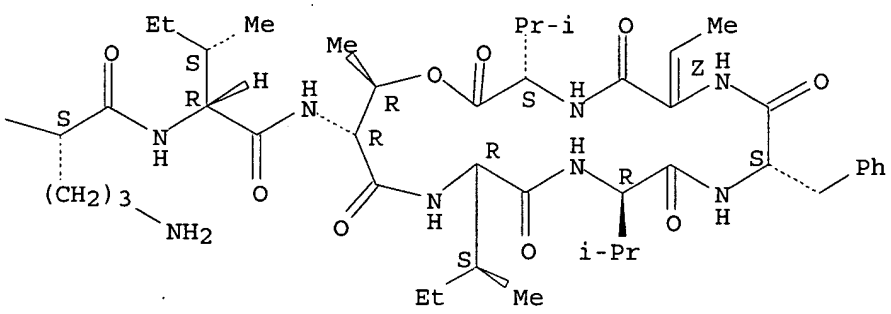
RN 847833-79-8 HCAPLUS
CN Kahalalide F, 1-[N-[4-[(aminoiminomethyl)amino]-1-oxobutyl]-D-valine]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



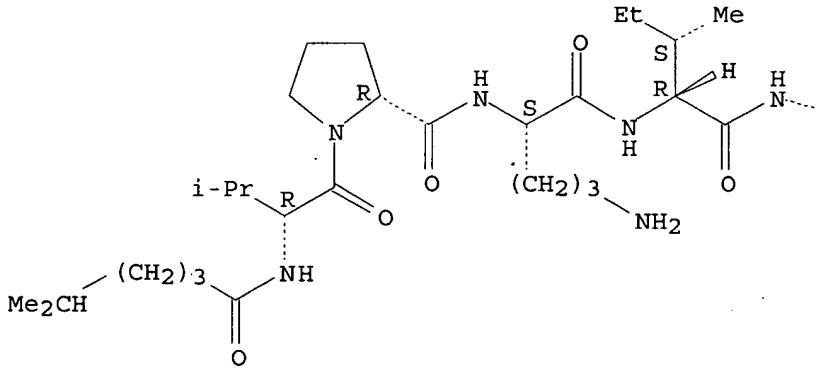
PAGE 1-B



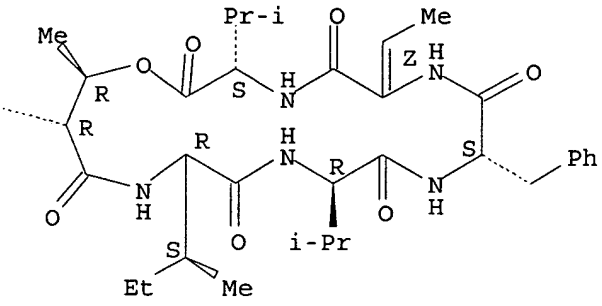
RN 847833-81-2 HCAPLUS
CN 4-13-Kahalalide F, 4-[N-(5-methyl-1-oxohexyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



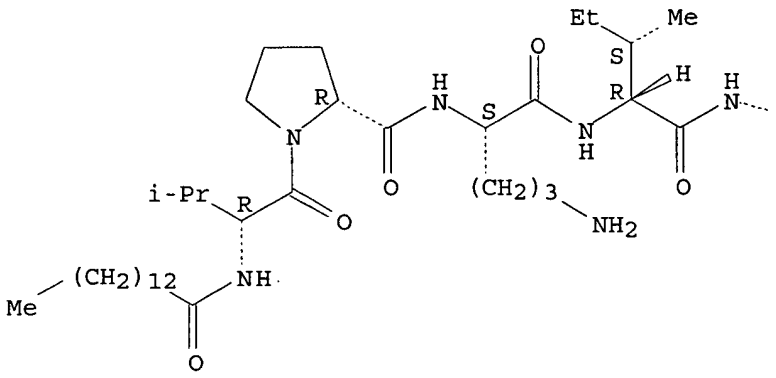
PAGE 1-B



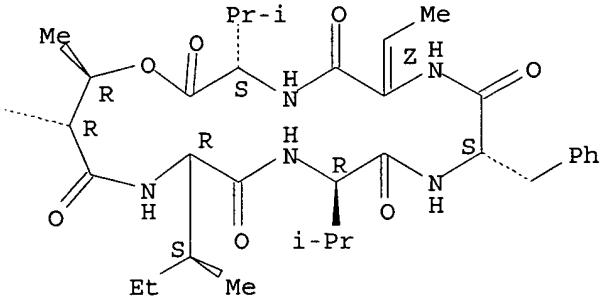
RN 847833-82-3 HCAPLUS
CN 4-13-Kahalalide F, 4-[N-(1-oxotetradecyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



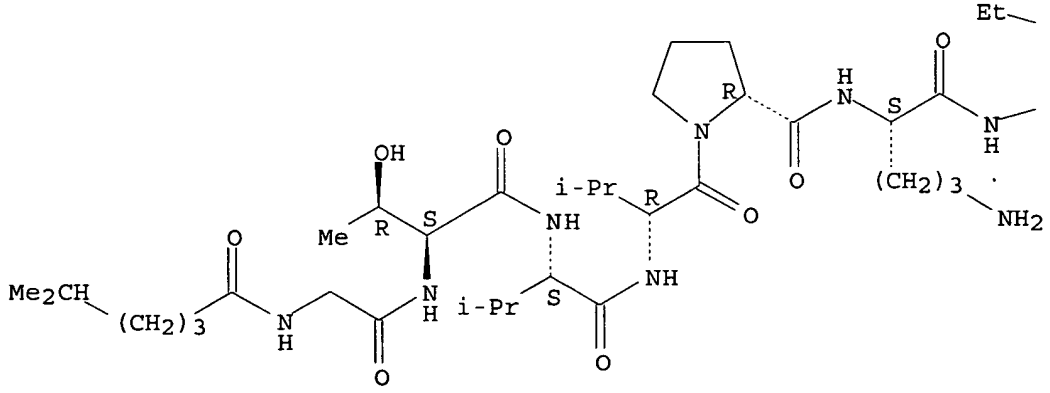
PAGE 1-B



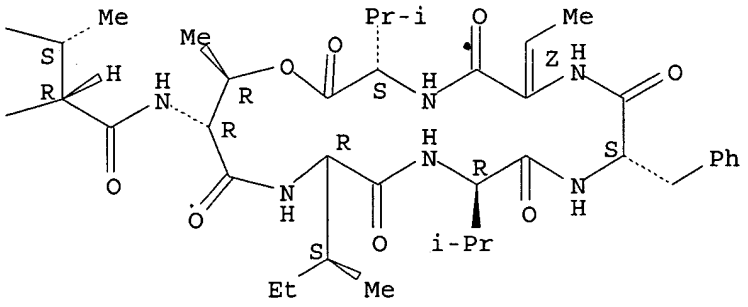
RN 847833-83-4 HCAPLUS
CN Kahalalide F, 1-[N-(5-methyl-1-oxohexyl)glycine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



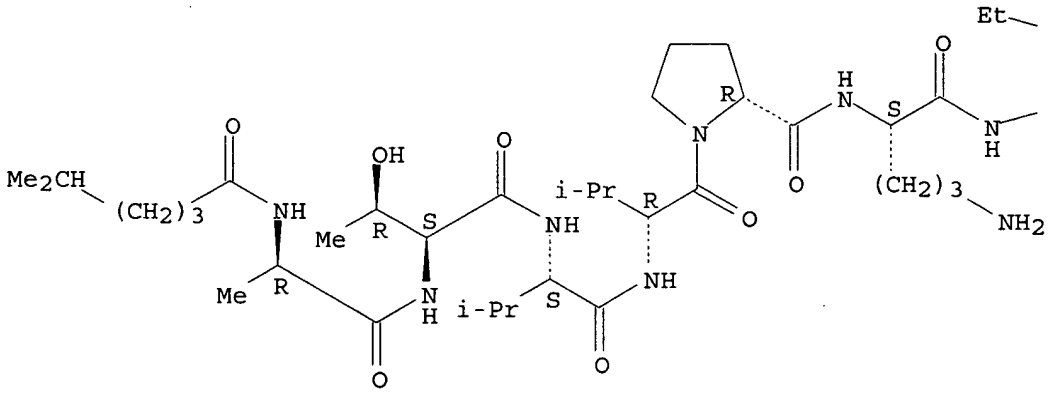
PAGE 1-B



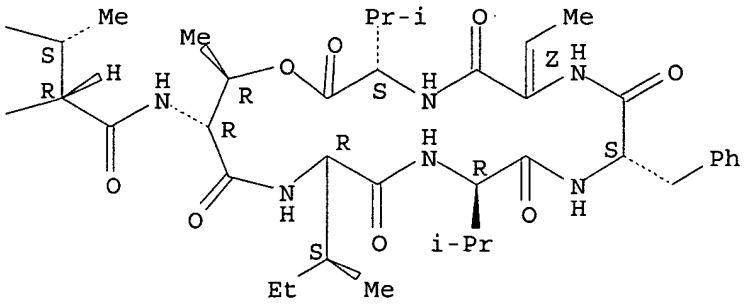
RN 847833-84-5 HCAPLUS
CN Kahalalide F, 1-[N-(5-methyl-1-oxohexyl)-D-alanine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

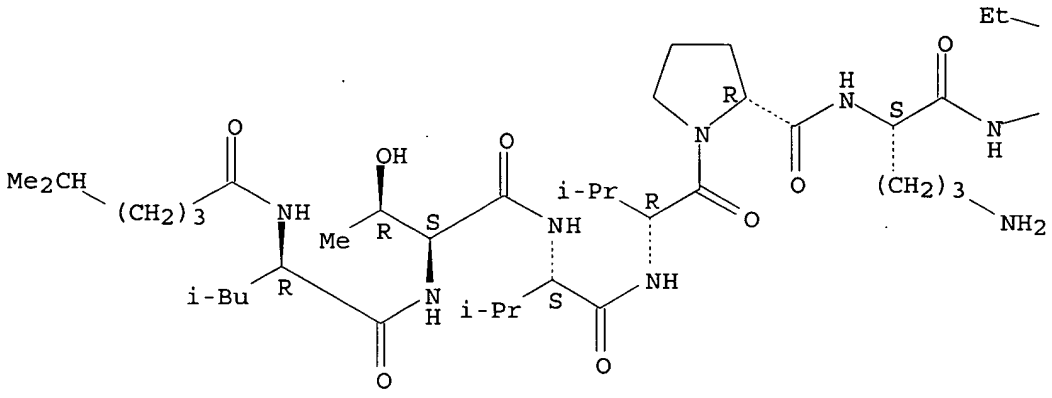


RN 847833-85-6 HCAPLUS

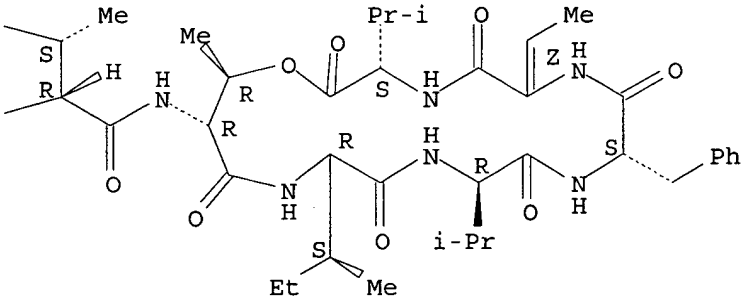
CN Kahalalide F, 1-[N-(5-methyl-1-oxohexyl)-D-leucine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



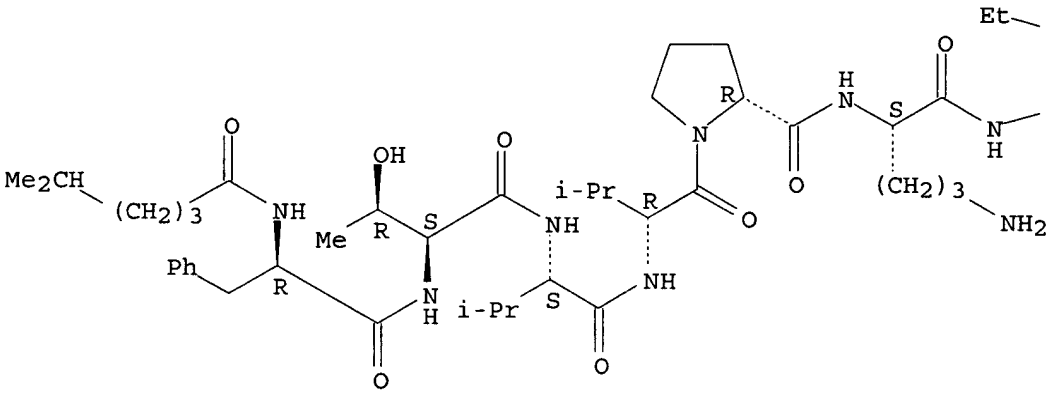
PAGE 1-B



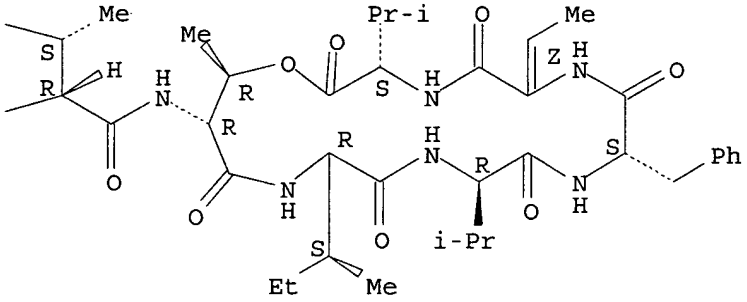
RN 847833-86-7 HCAPLUS
CN Kahalalide F, 1-[N-(5-methyl-1-oxohexyl)-D-phenylalanine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



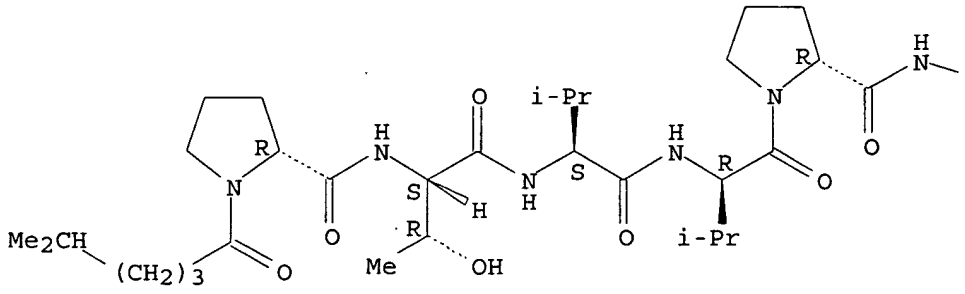
PAGE 1-B



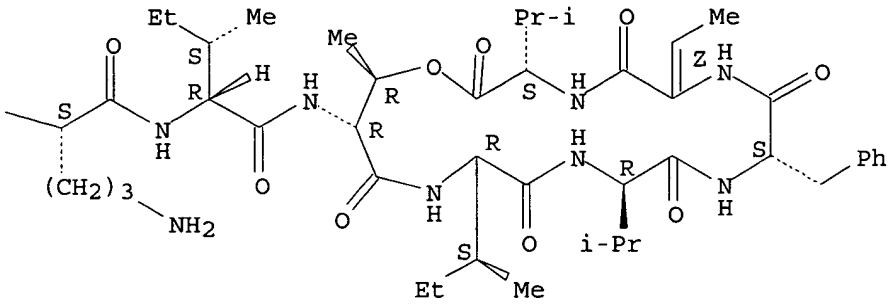
RN 847833-87-8 HCAPLUS
CN Kahalalide F, 1-[1-(5-methyl-1-oxohexyl)-D-proline]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



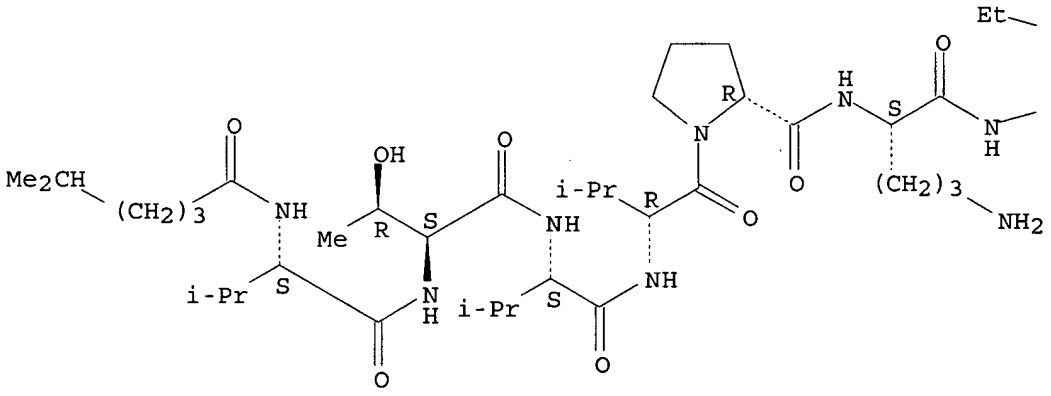
PAGE 1-B



RN 847833-88-9 HCAPLUS
CN Kahalalide F, 1-[N-(5-methyl-1-oxohexyl)-L-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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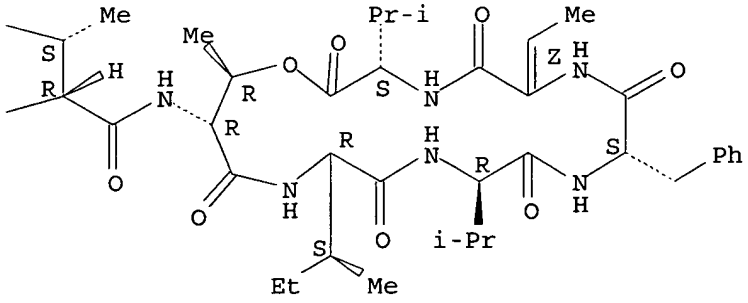
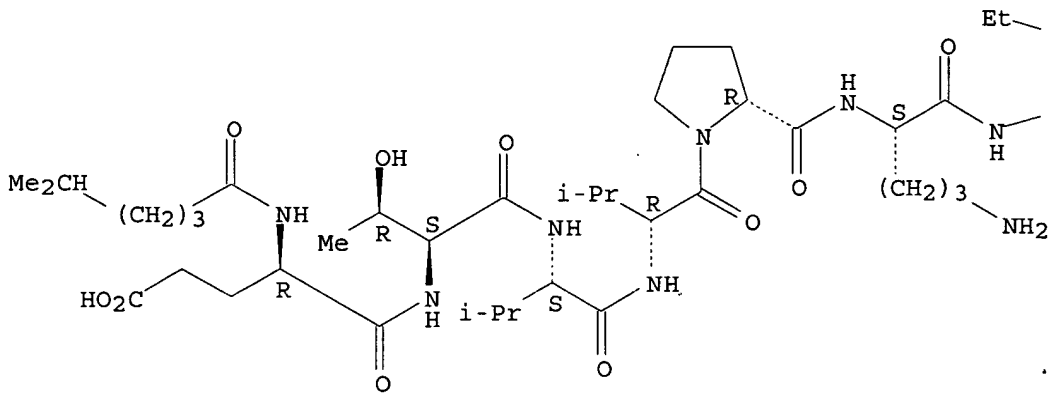


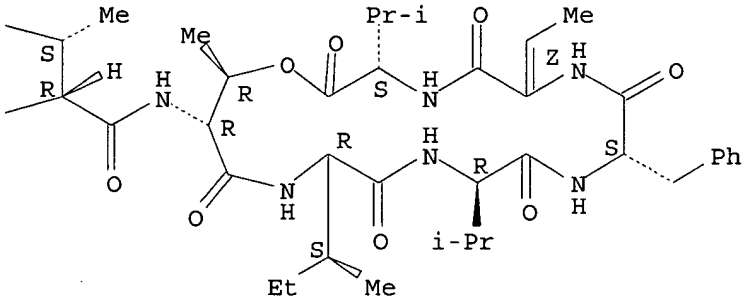
RN 847833-89-0 HCAPLUS
CN Kahalalide F, 1-[N-(5-methyl-1-oxohexyl)-D-glutamic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



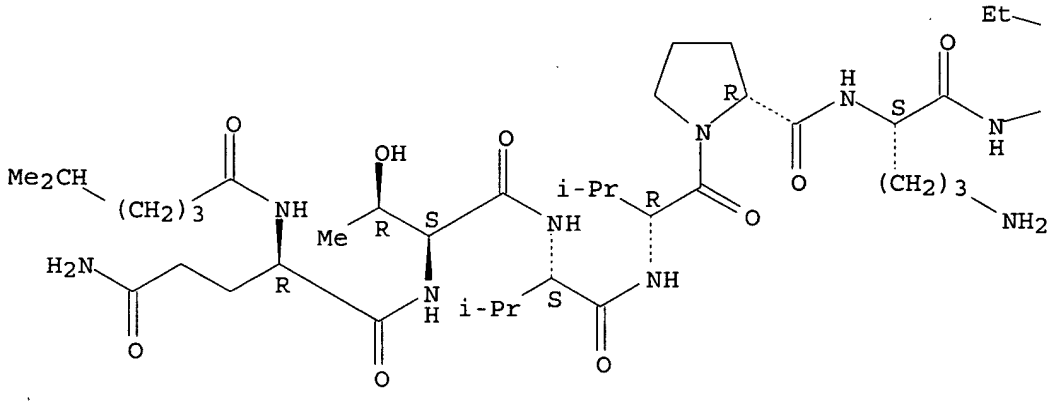
PAGE 1-B



RN 847833-90-3 HCAPLUS
CN Kahalalide F, 1-[N2-(5-methyl-1-oxohexyl)-D-glutamine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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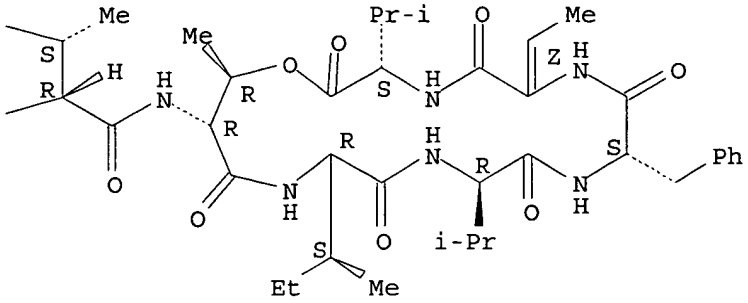
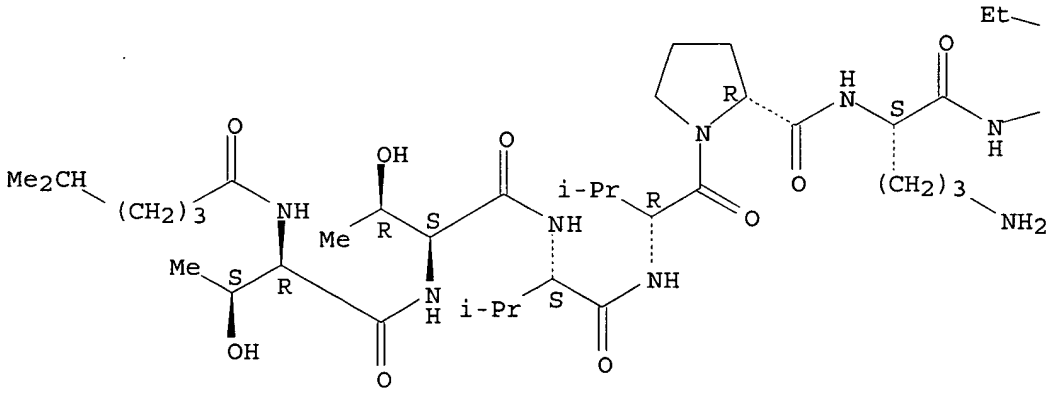


RN 847833-91-4 HCAPLUS
CN Kahalalide F, 1-[N-(5-methyl-1-oxohexyl)-D-threonine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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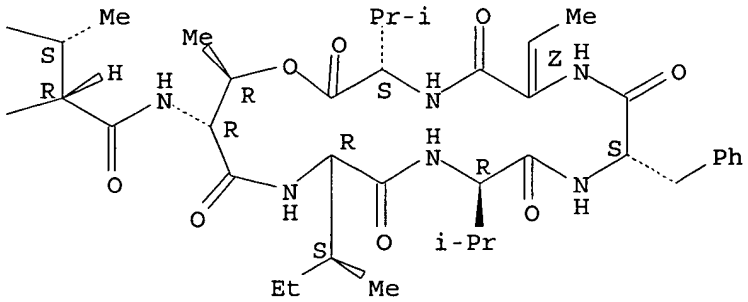
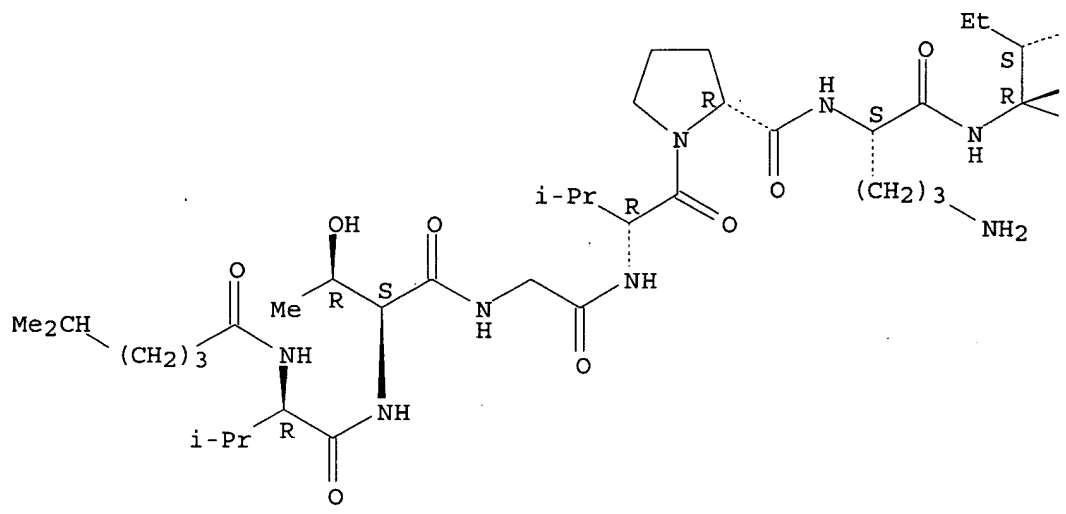


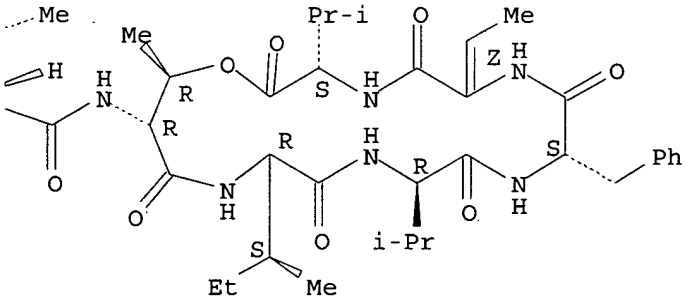
RN 847833-92-5 HCAPLUS
CN Kahalalide F, 3-glycine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



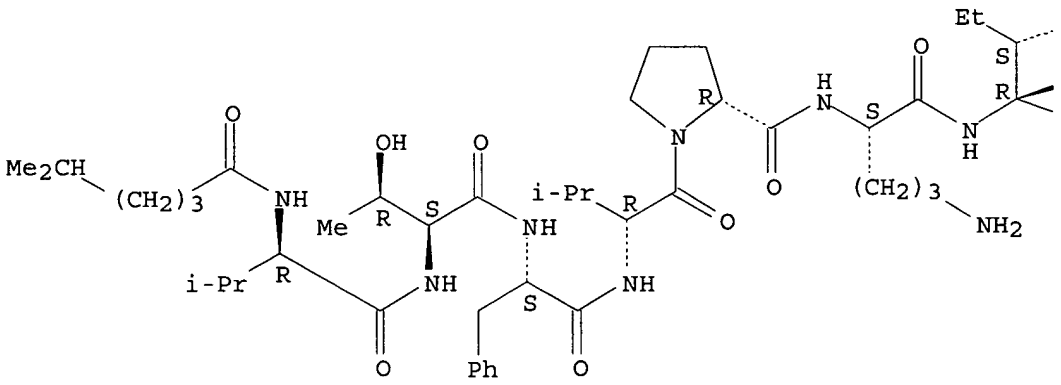
PAGE 1-B



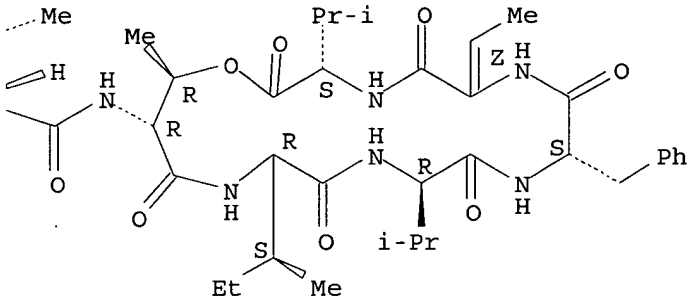
RN 847833-93-6 HCAPLUS
CN Kahalalide F, 3-L-phenylalanine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



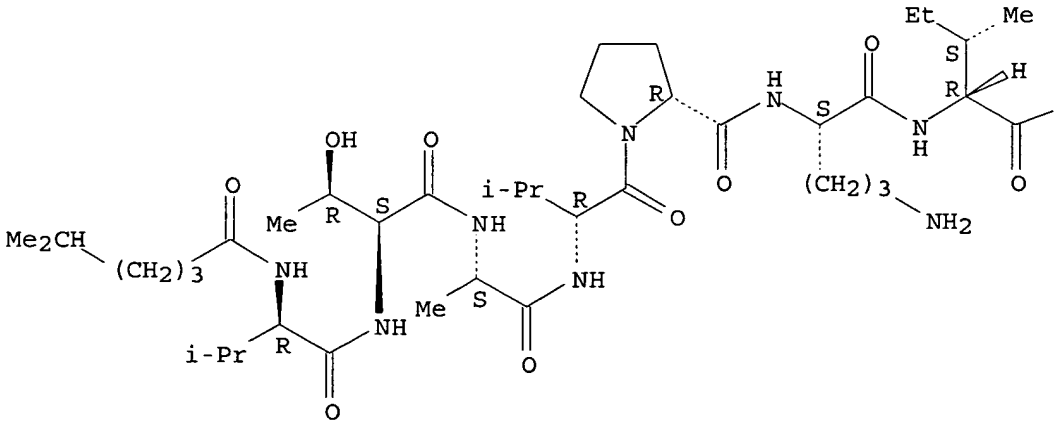
PAGE 1-B



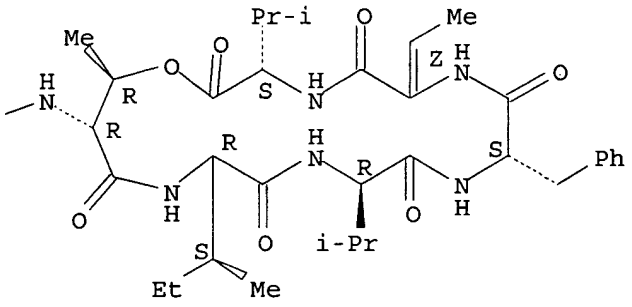
RN 847833-94-7 HCAPLUS
CN Kahalalide F, 3-L-alanine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



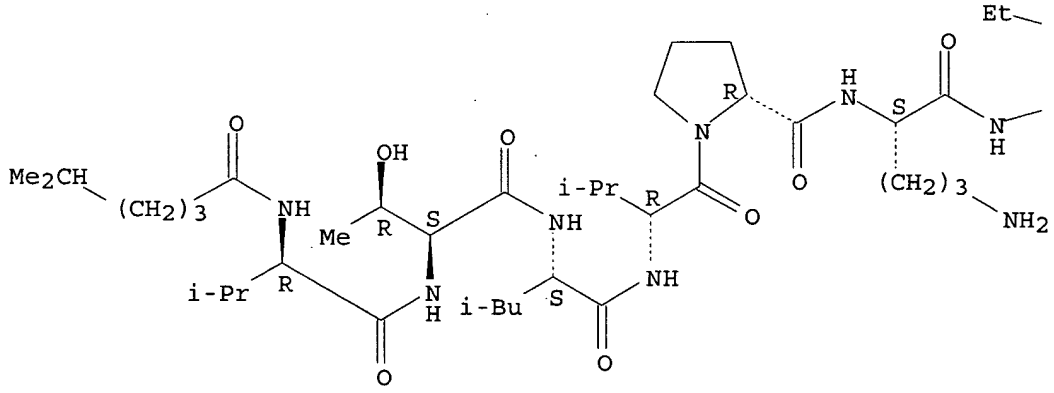
PAGE 1-B



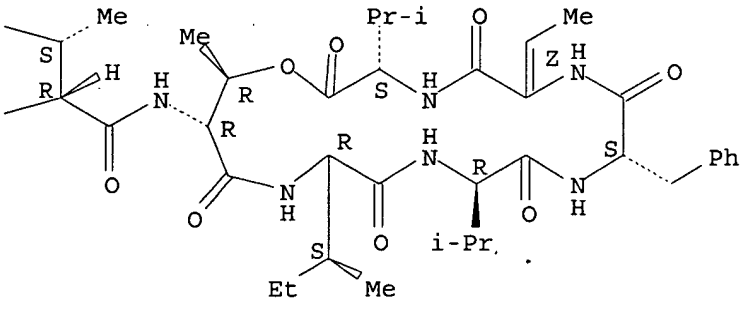
RN. 847833-95-8 HCAPLUS
CN Kahalalide F, 3-L-leucine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



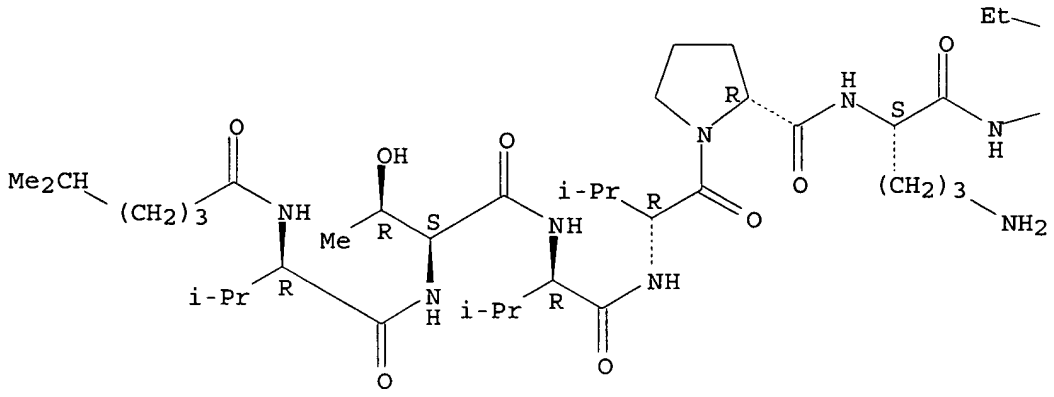
PAGE 1-B



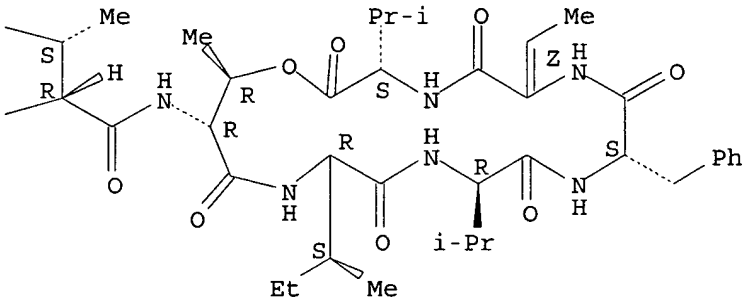
RN 847833-96-9 HCAPLUS
CN Kahalalide F, 3-D-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



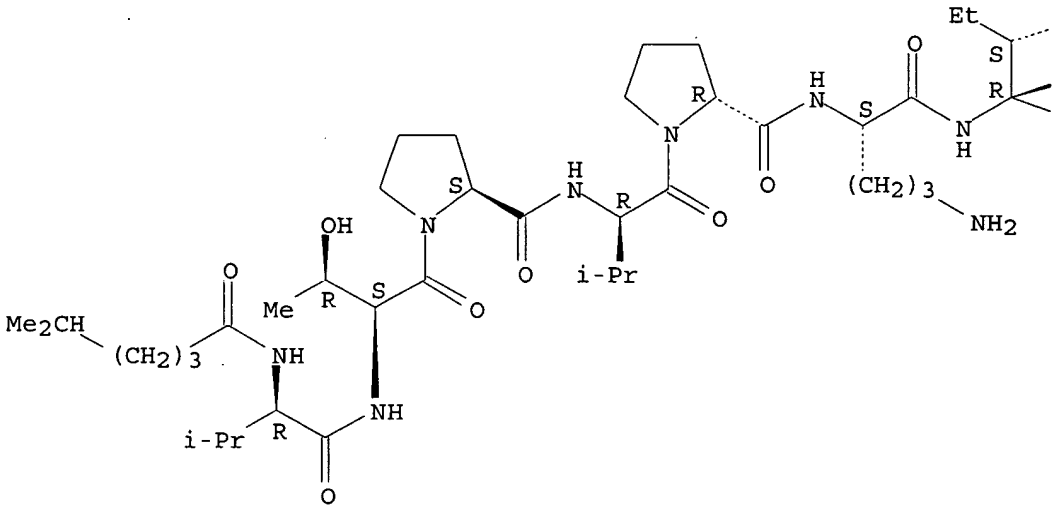
PAGE 1-B



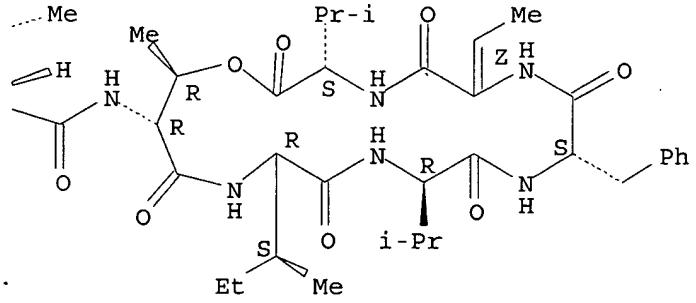
RN 847833-97-0 HCAPLUS
CN Kahalalide F, 3-L-proline- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



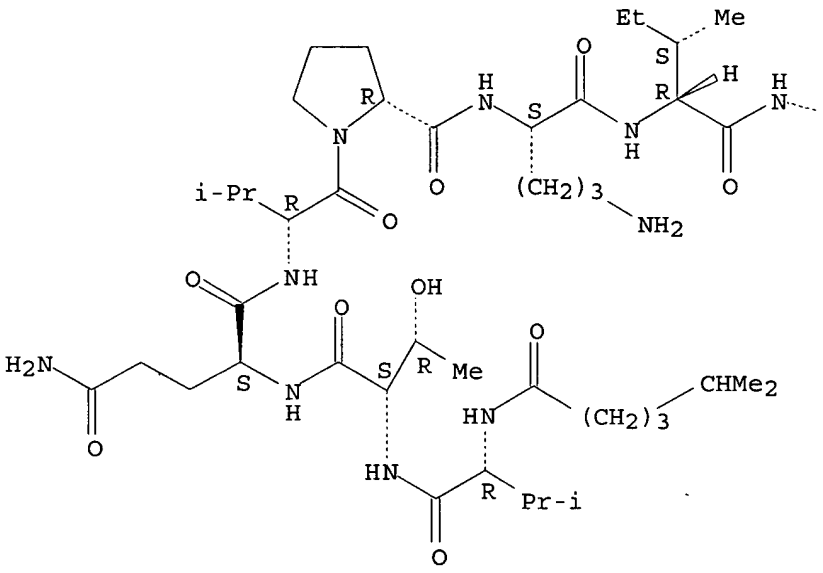
PAGE 1-B



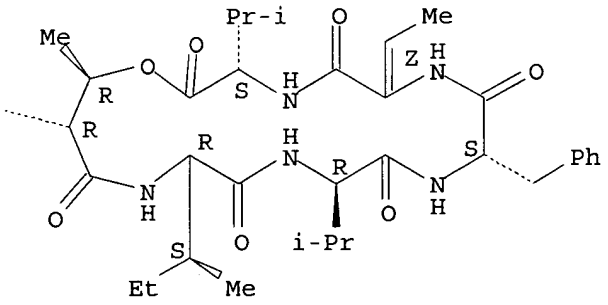
RN 847833-98-1 HCAPLUS
CN Kahalalide F, 3-L-glutamine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



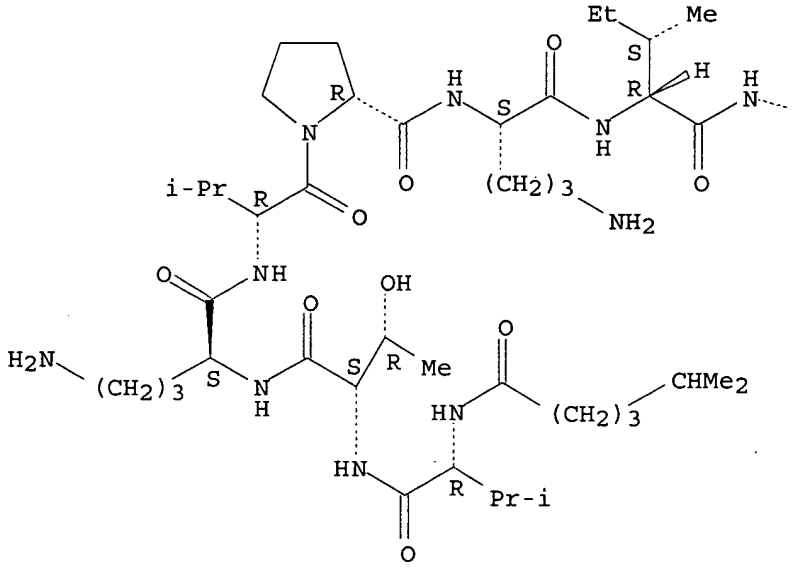
PAGE 1-B



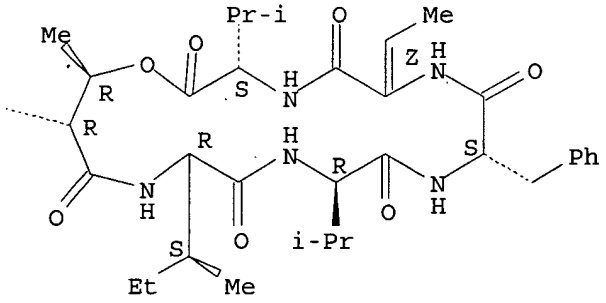
RN 847833-99-2 HCAPLUS
CN Kahalalide F, 3-L-ornithine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



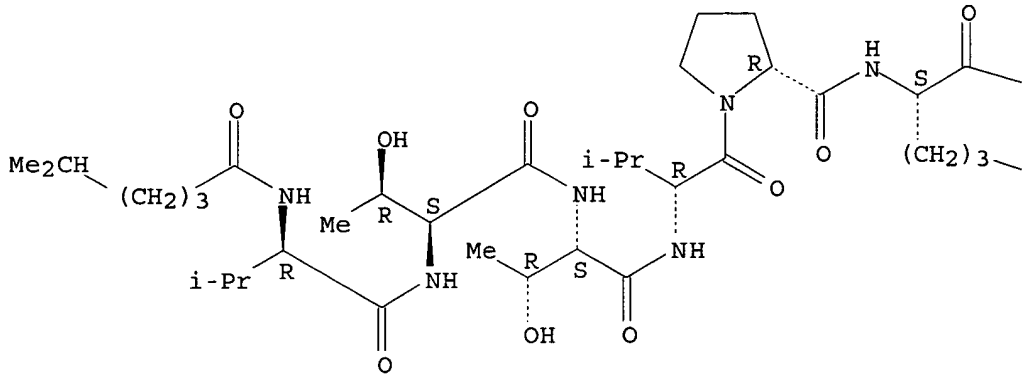
PAGE 1-B



RN 847834-00-8 HCAPLUS
CN Kahalalide F, 3-L-threonine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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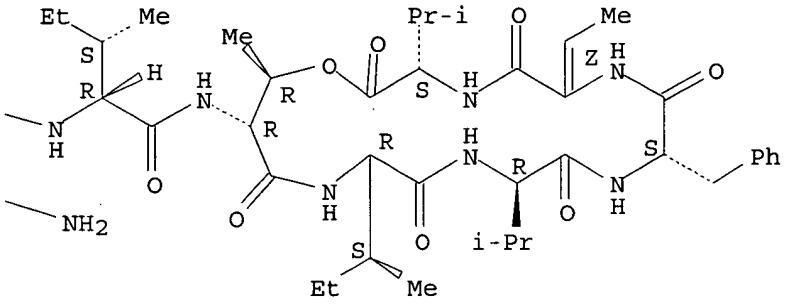
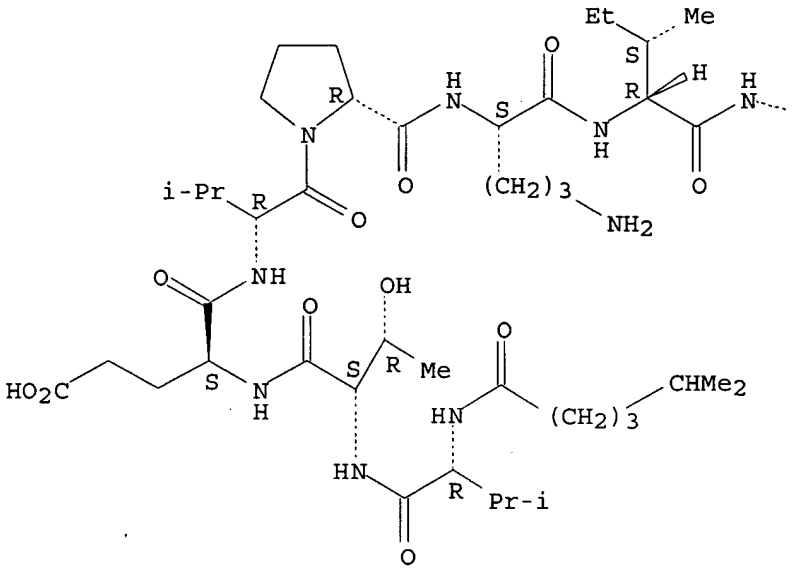


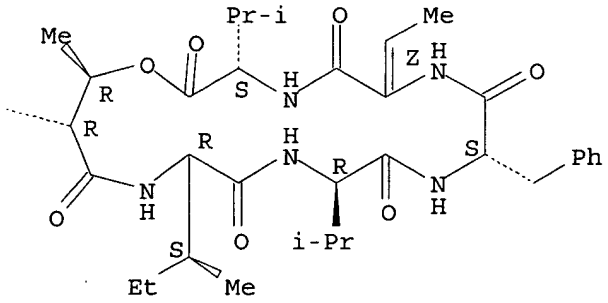
RN 847834-01-9 HCAPLUS
CN Kahalalide F, 3-L-glutamic acid- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



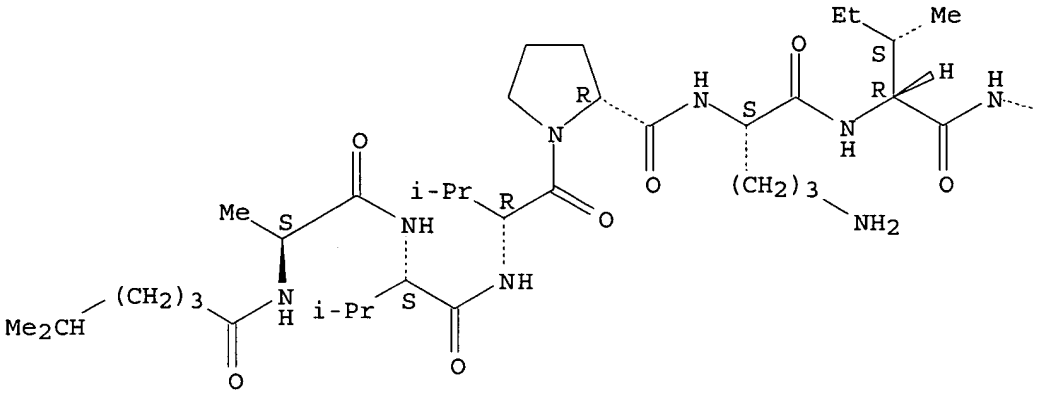
PAGE 1-B



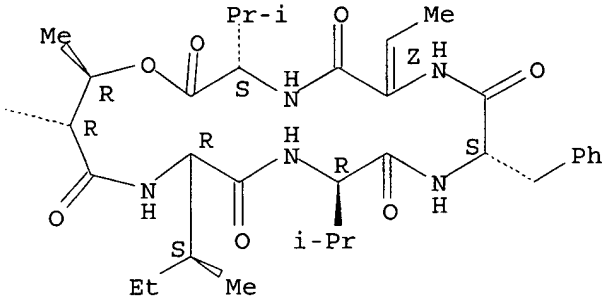
RN 847834-02-0 HCAPLUS
CN 2-13-Kahalalide F, 2-[N-(5-methyl-1-oxohexyl)-L-alanine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



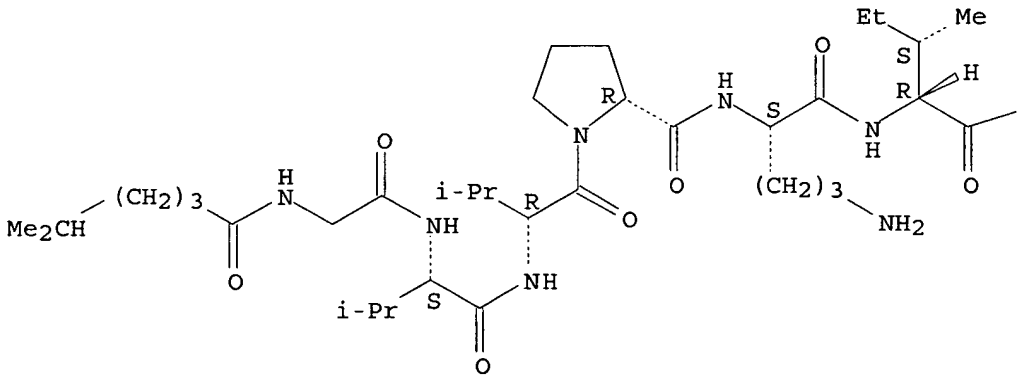
PAGE 1-B



RN 847834-03-1 HCAPLUS
CN 2-13-Kahalalide F, 2-[N-(5-methyl-1-oxohexyl)glycine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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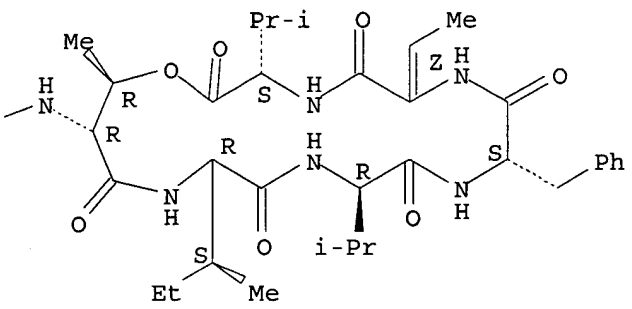
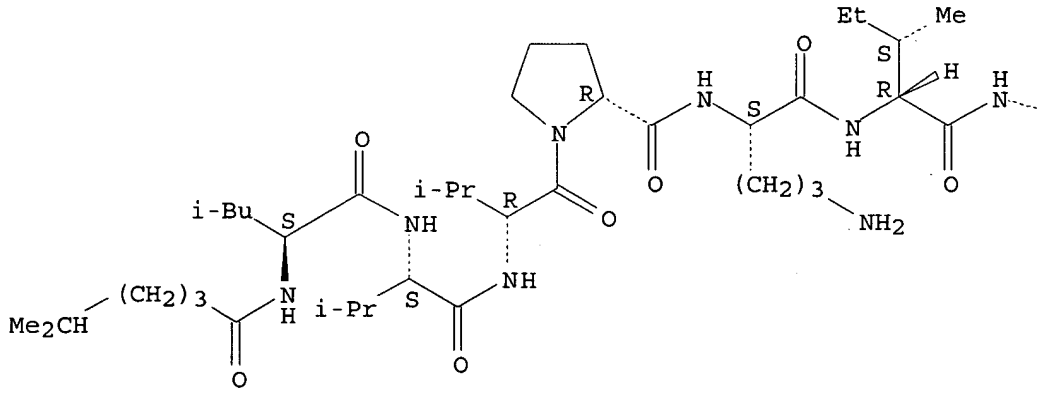


RN 847834-04-2 HCAPLUS
CN 2-13-Kahalalide F, 2-[N-(5-methyl-1-oxohexyl)-L-leucine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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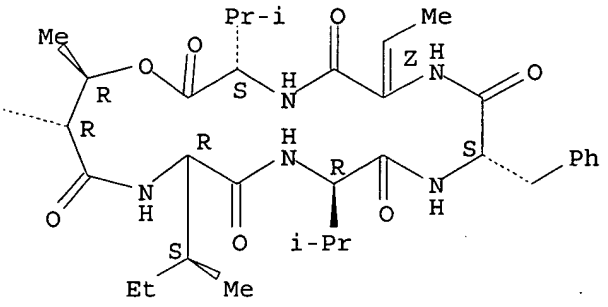
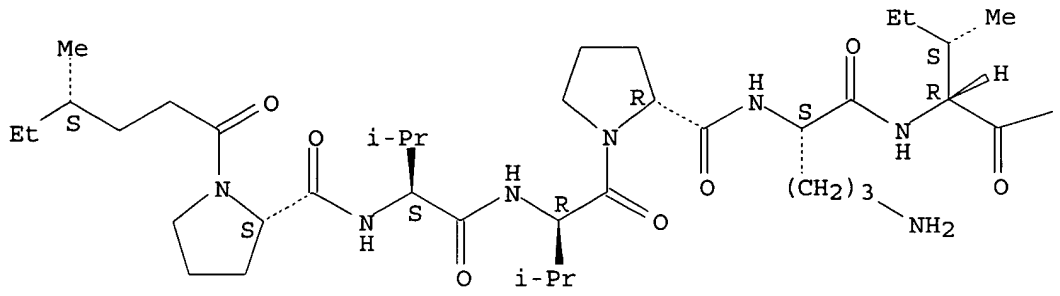


RN 847834-05-3 HCAPLUS
CN 2-13-Kahalalide F, 2-[1-[(4S)-4-methyl-1-oxohexyl]-L-proline]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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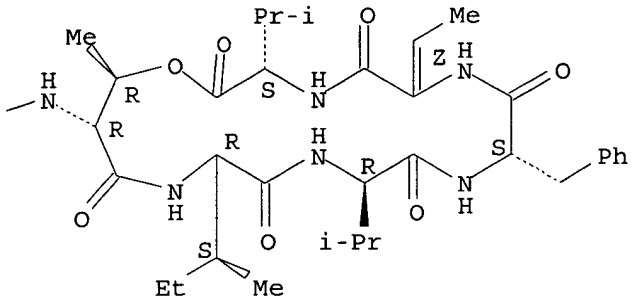
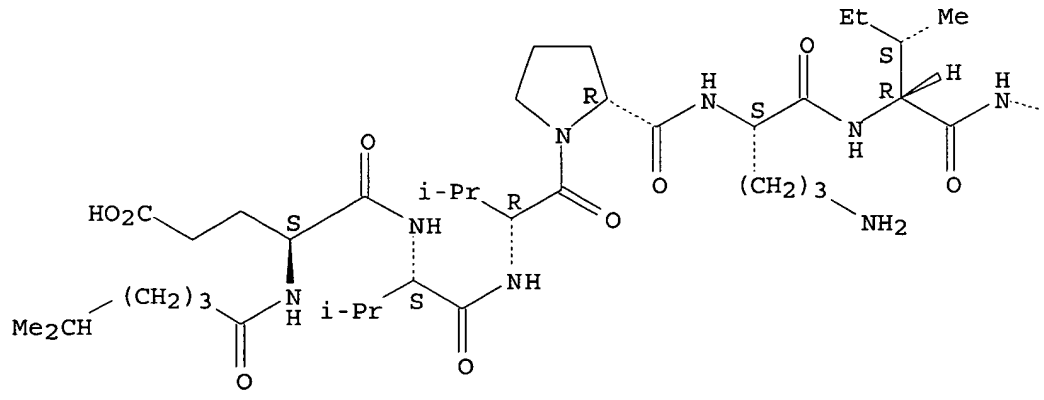


RN 847834-06-4 HCAPLUS
CN 2-13-Kahalalide F, 2-[N-(5-methyl-1-oxohexyl)-L-glutamic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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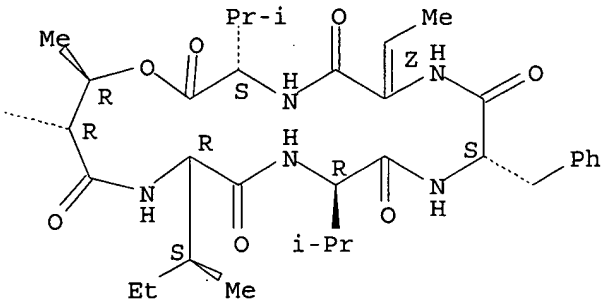
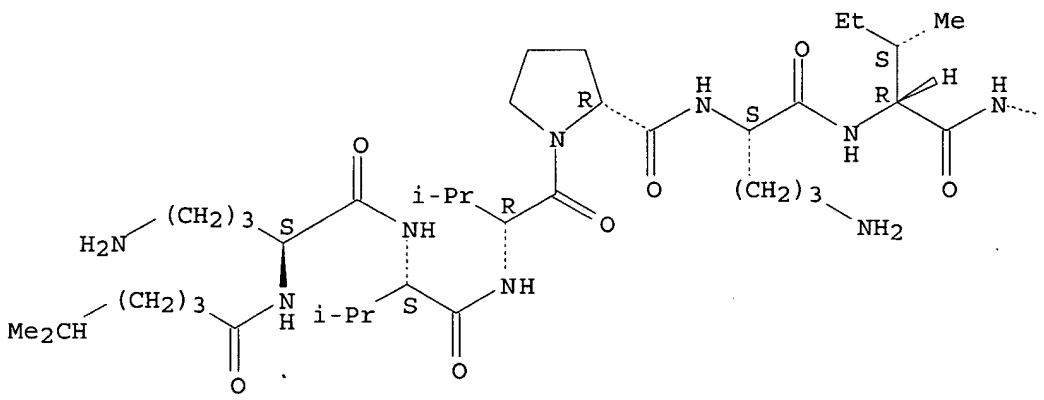


RN 847834-07-5 HCAPLUS
CN 2-13-Kahalalide F, 2-[N2-(5-methyl-1-oxohexyl)-L-ornithine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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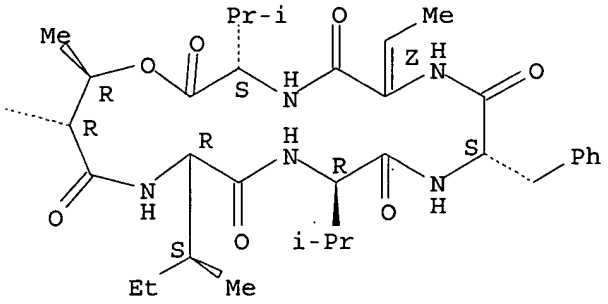
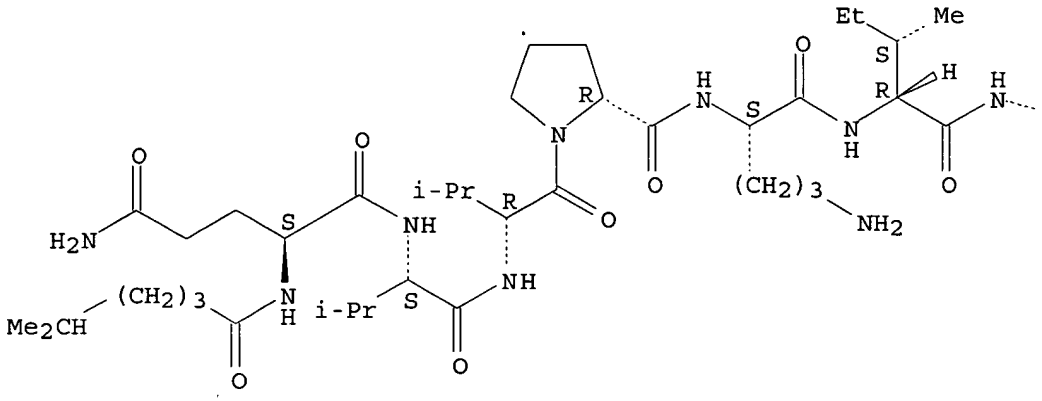


RN 847834-08-6 HCAPLUS
CN 2-13-Kahalalide F, 2-[N2-(5-methyl-1-oxohexyl)-L-glutamine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



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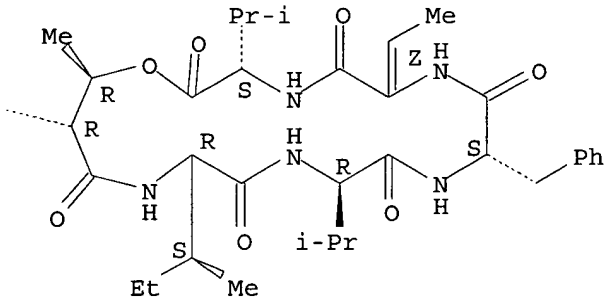
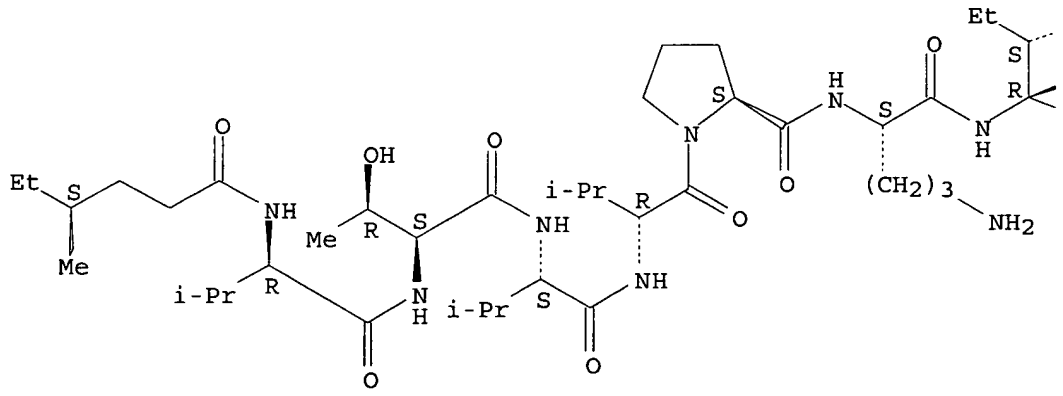


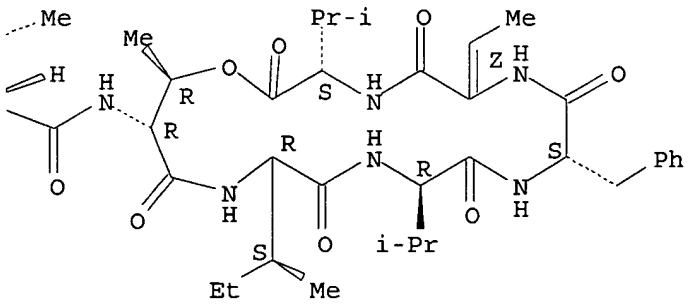
RN 847834-09-7 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-5-L-proline- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



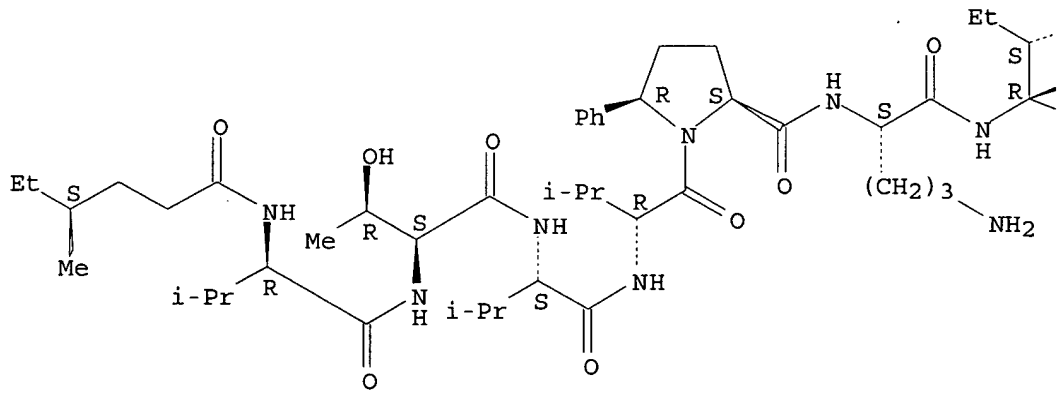
PAGE 1-B



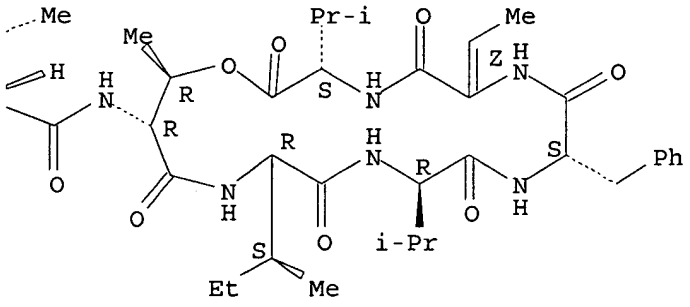
RN 847834-12-2 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-5-[(5R)-5-phenyl-L-proline]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



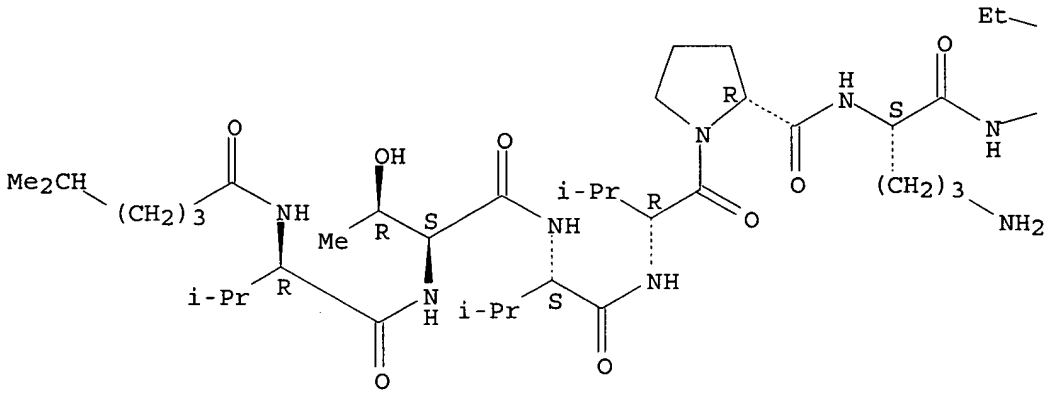
PAGE 1-B



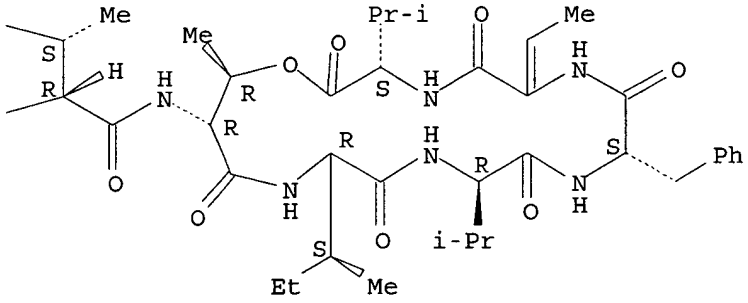
RN 847834-17-7 HCAPLUS
CN Kahalalide F, 12-(2-amino-2-butenoic acid)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



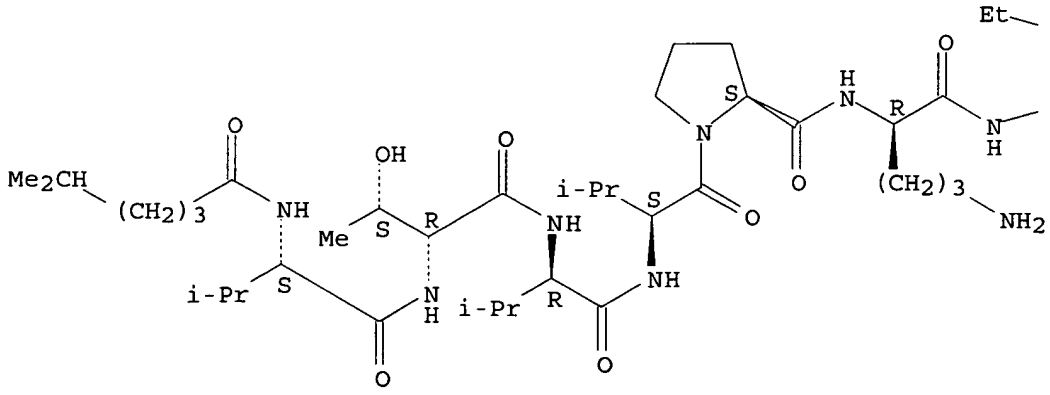
PAGE 1-B



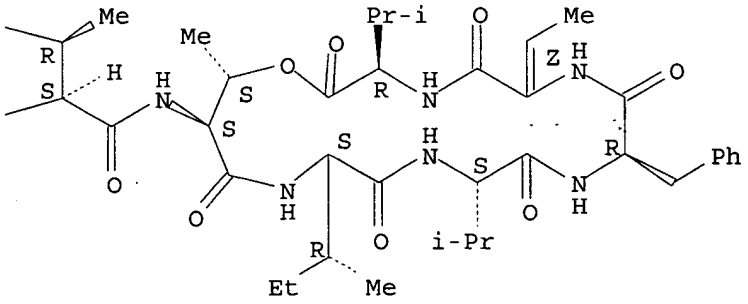
RN 847834-19-9 HCAPLUS
CN enantio-Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



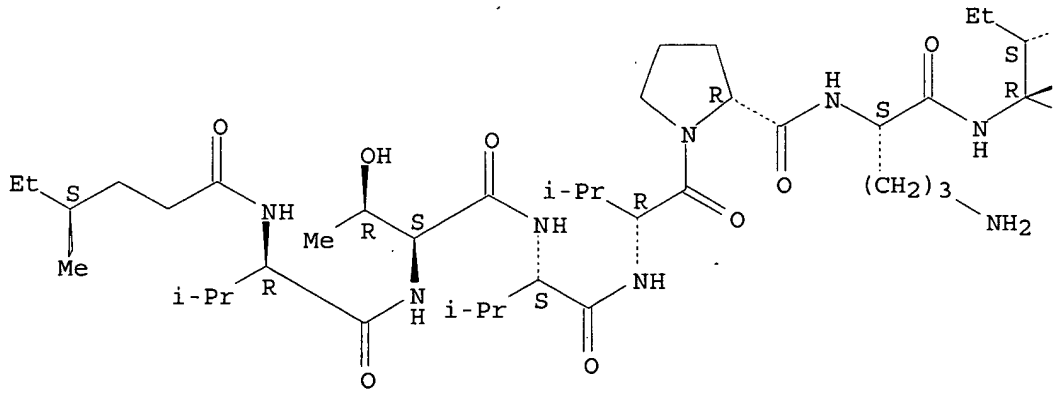
PAGE 1-B



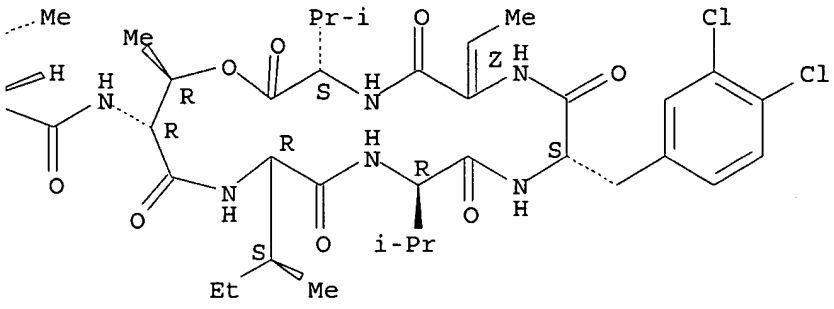
RN 847834-20-2 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-(3,4-dichloro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

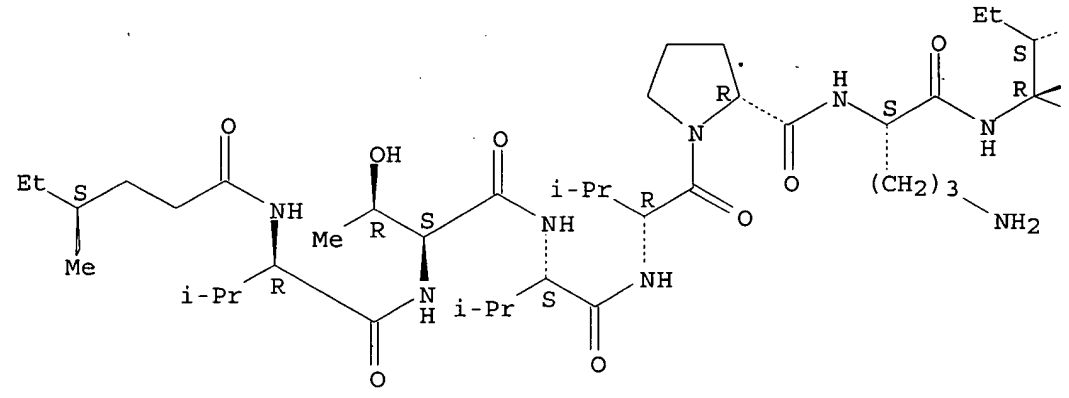


RN 847834-21-3 HCAPLUS

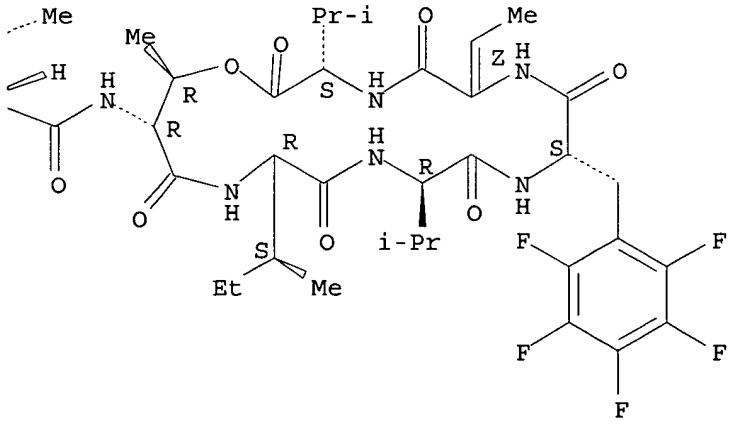
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-(2,3,4,5,6-pentafluoro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



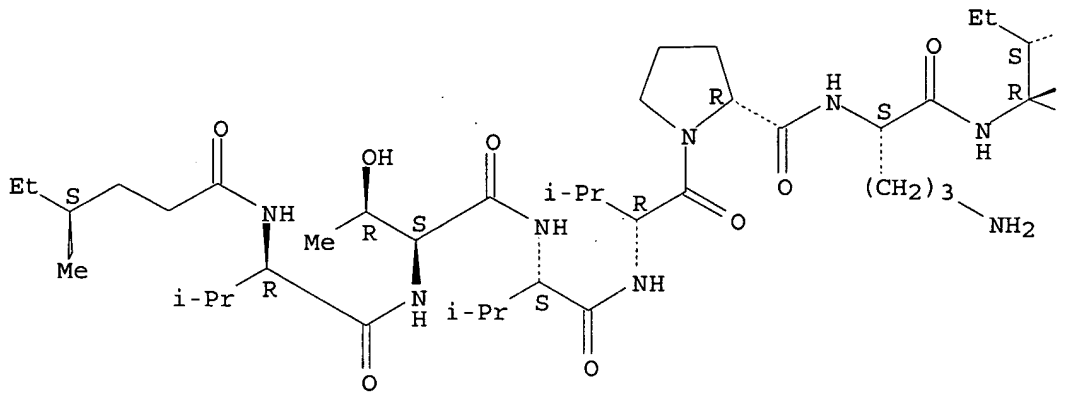
PAGE 1-B



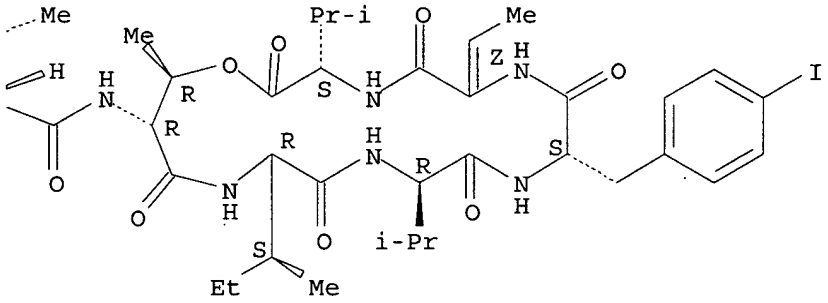
RN 847834-22-4 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-(4-iodo-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



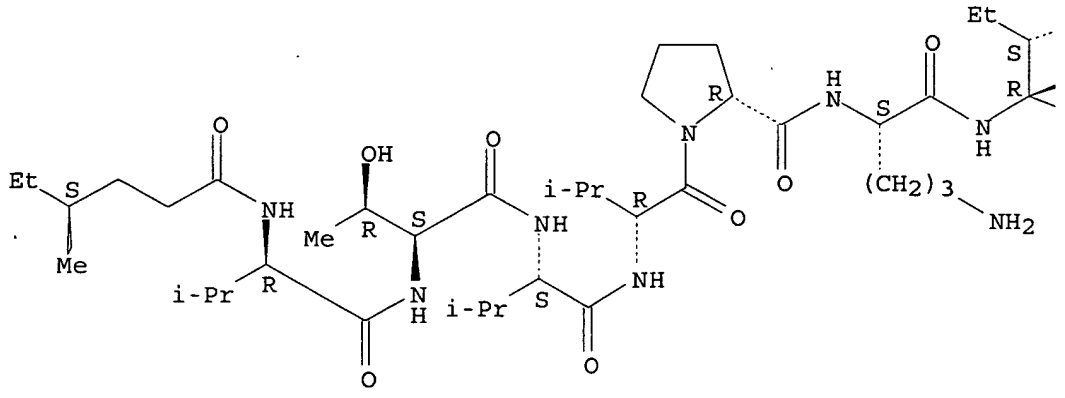
PAGE 1-B



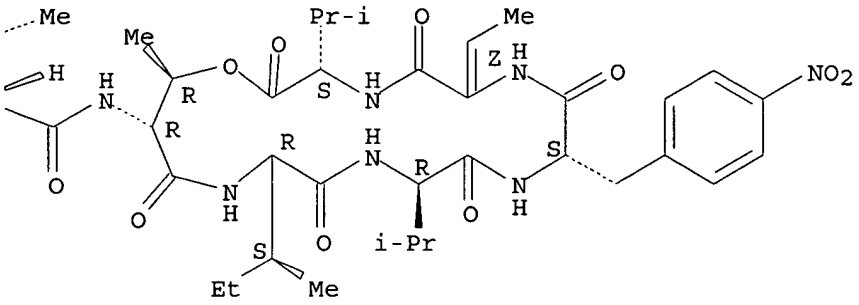
RN 847834-23-5 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-(4-nitro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



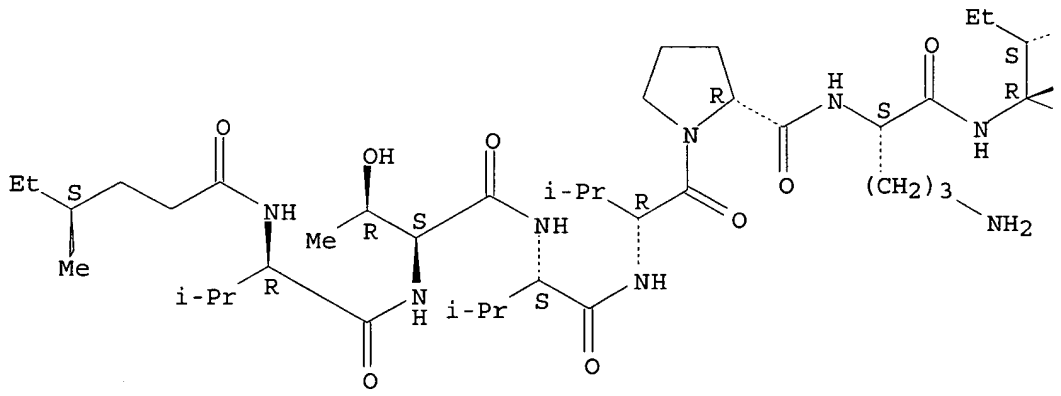
PAGE 1-B



RN 847834-24-6 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-(4-fluoro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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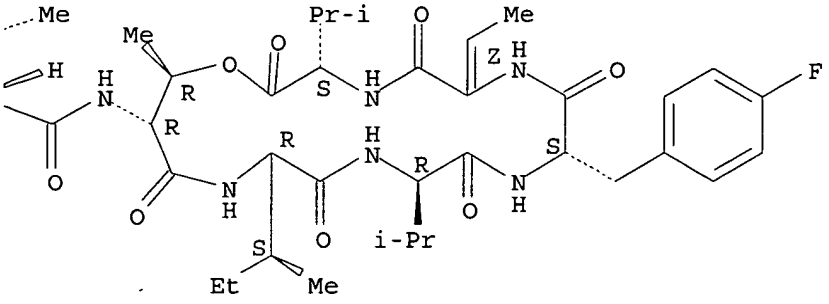
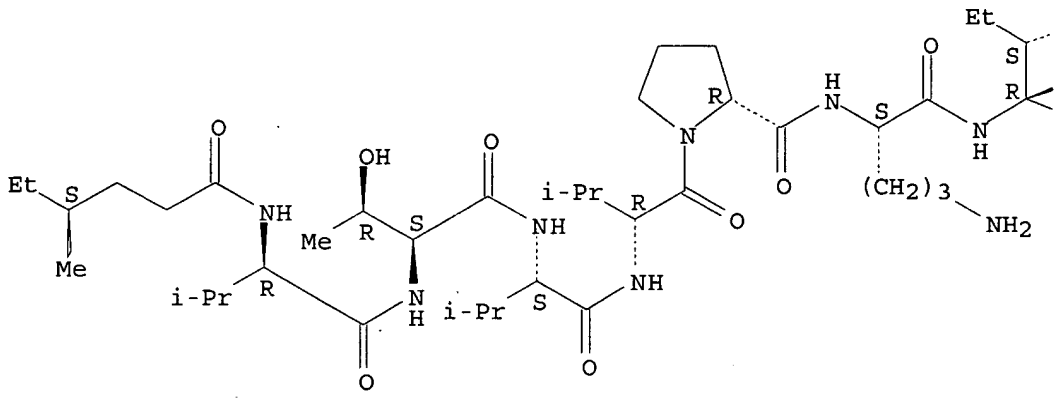


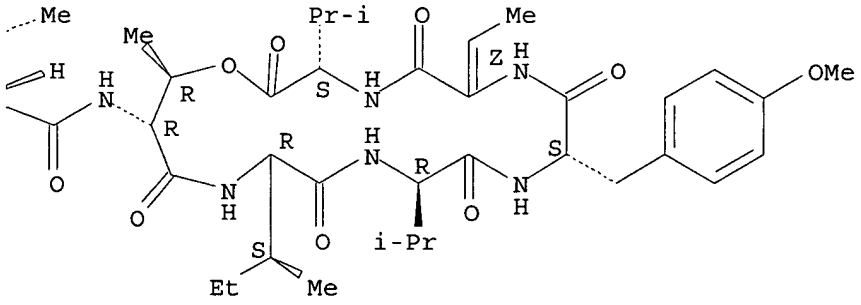
RN 847834-25-7 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-(O-methyl-L-tyrosine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



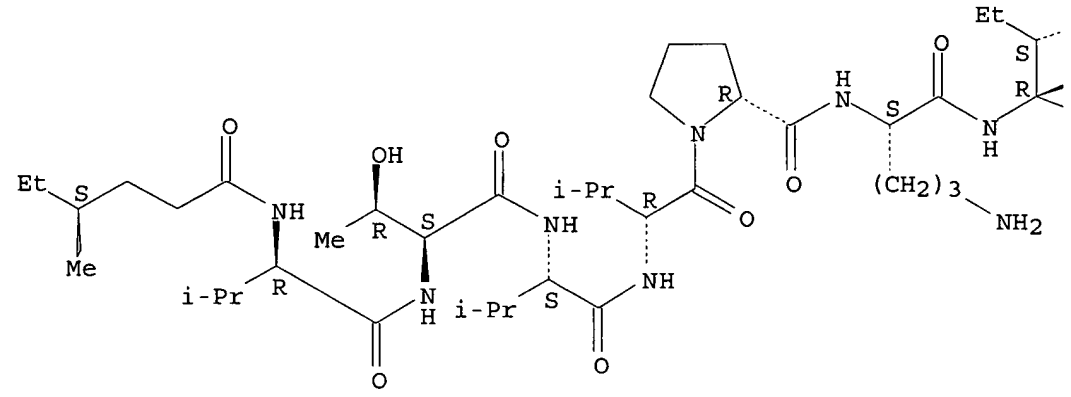
PAGE 1-B



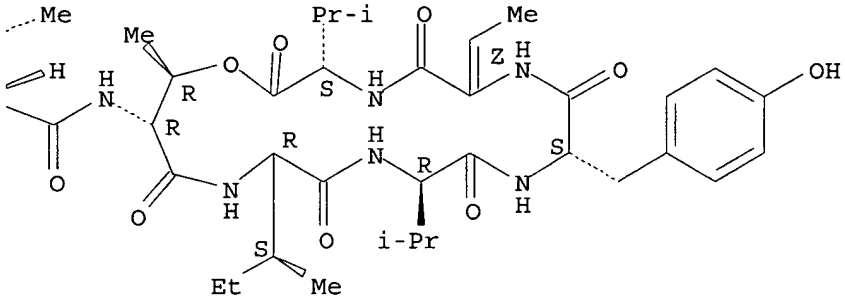
RN 847834-28-0 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-L-tyrosine-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



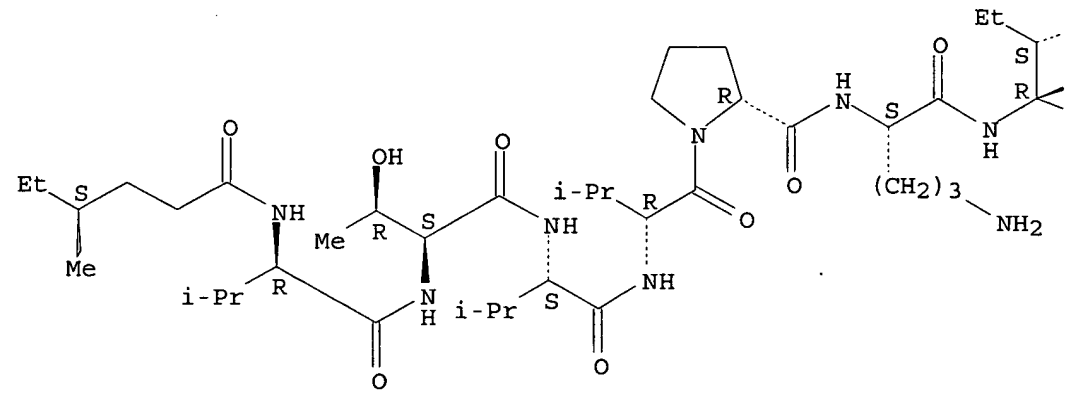
PAGE 1-B



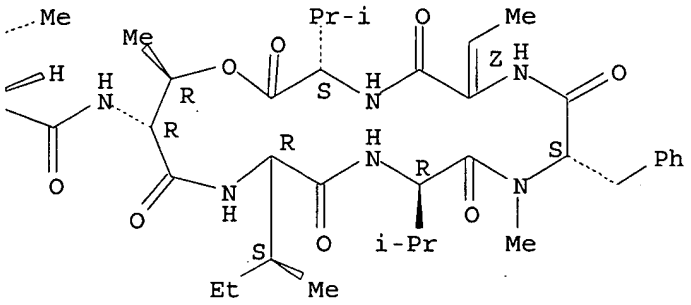
RN 847834-30-4 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-11-(N-methyl-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



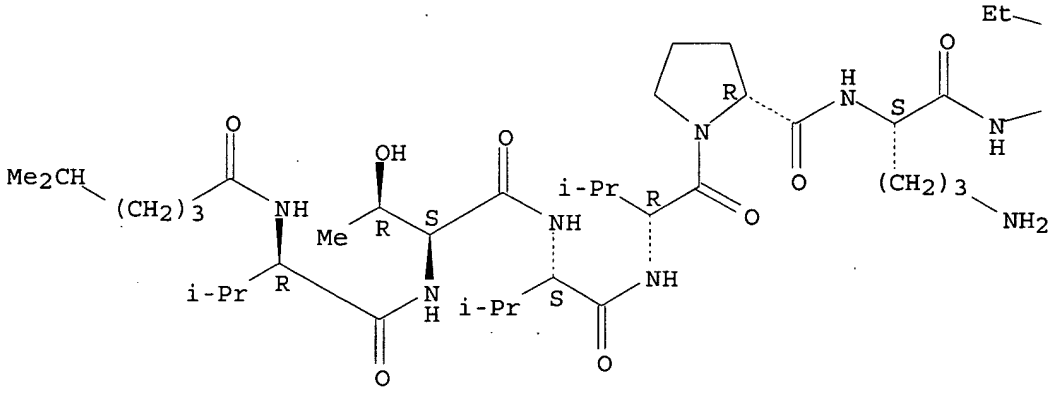
PAGE 1-B



RN 847834-31-5 HCAPLUS
CN Kahalalide F, 11-(2-chloro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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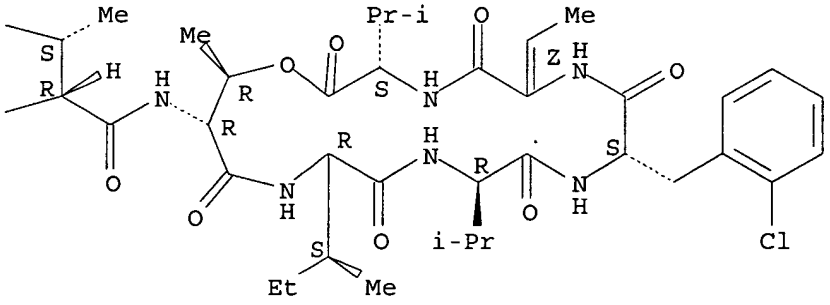
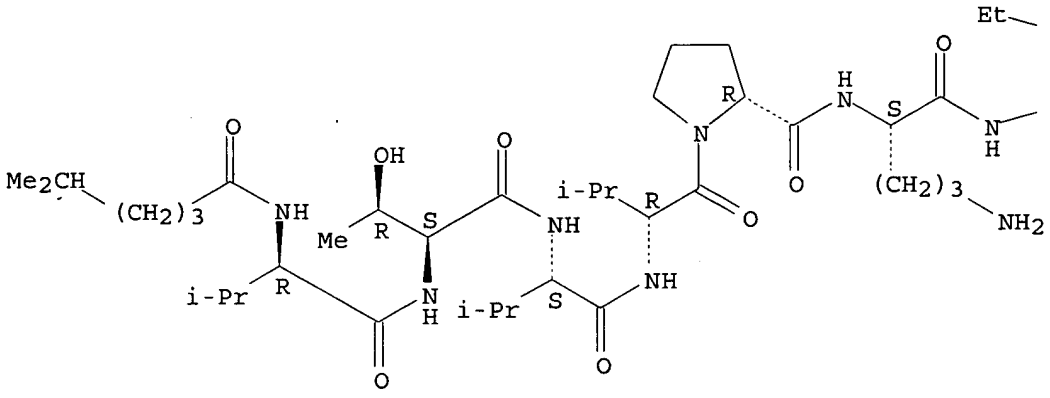


RN 847834-32-6 HCAPLUS
CN Kahalalide F, 11-(3-chloro-L-phenylalanine)- (9CI) (CA INDEX NAME)

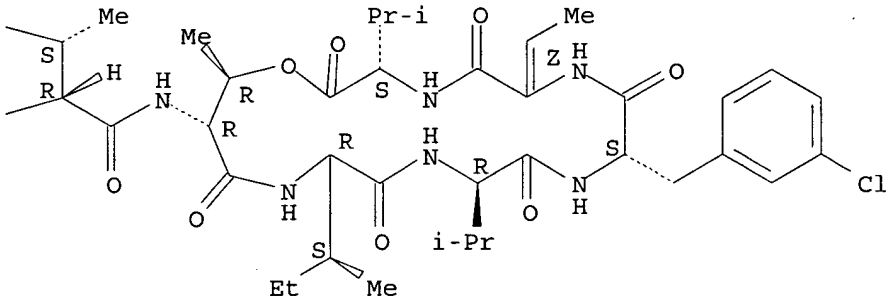
Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



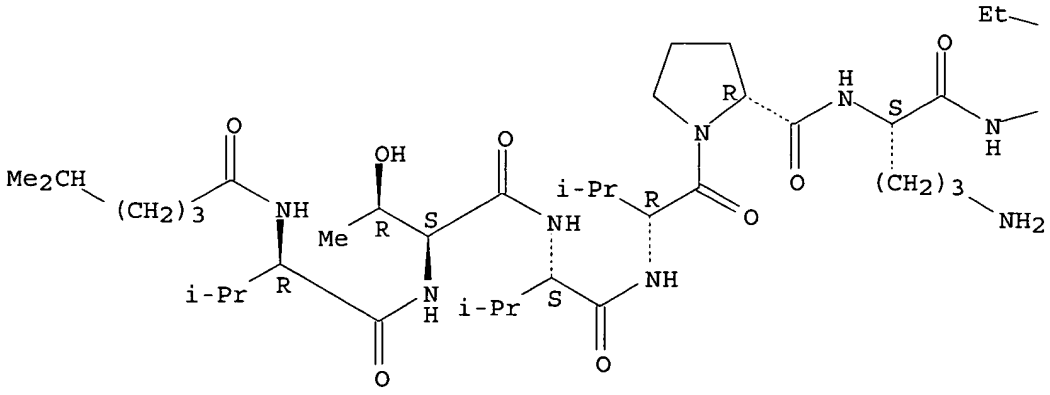
PAGE 1-B



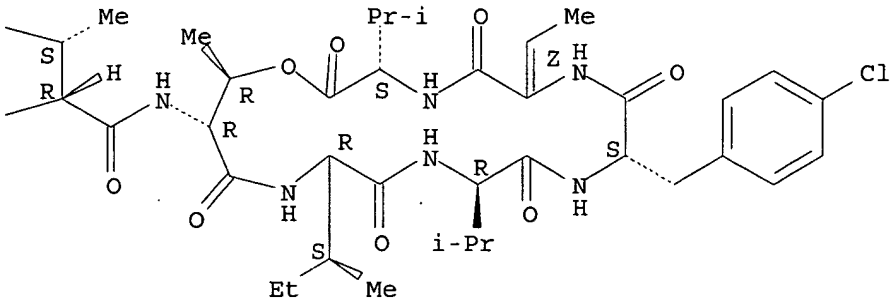
RN 847834-33-7 HCAPLUS
CN Kahalalide F, 11-(4-chloro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



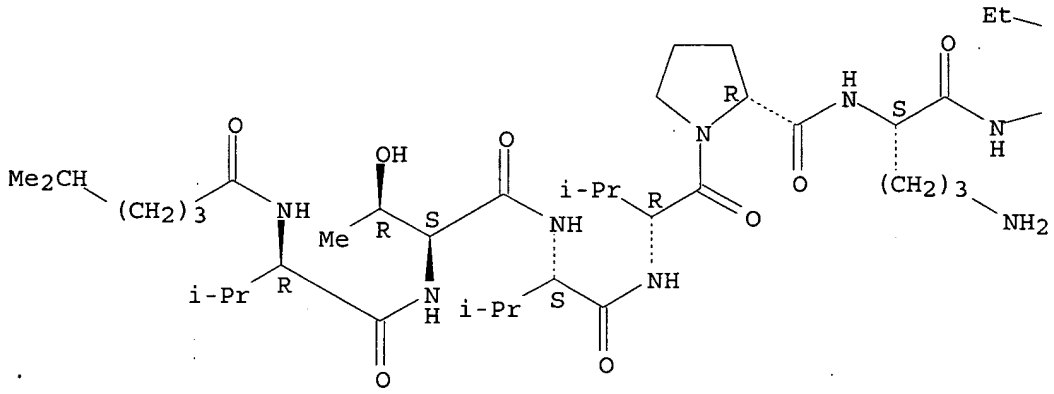
PAGE 1-B



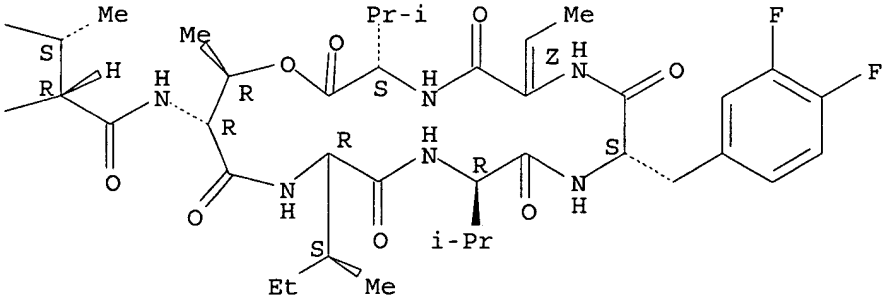
RN 847834-34-8 HCAPLUS
CN Kahalalide F, 11-(3,4-difluoro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

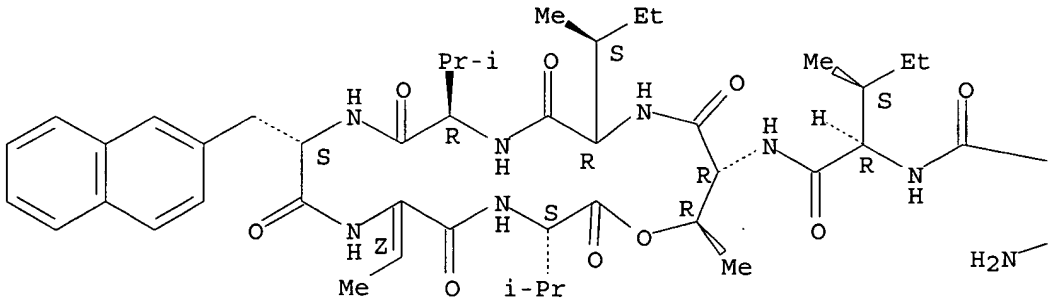


RN 847834-35-9 HCAPLUS
CN Kahalalide F, 11-[3-(2-naphthalenyl)-L-alanine]- (9CI) (CA INDEX NAME)

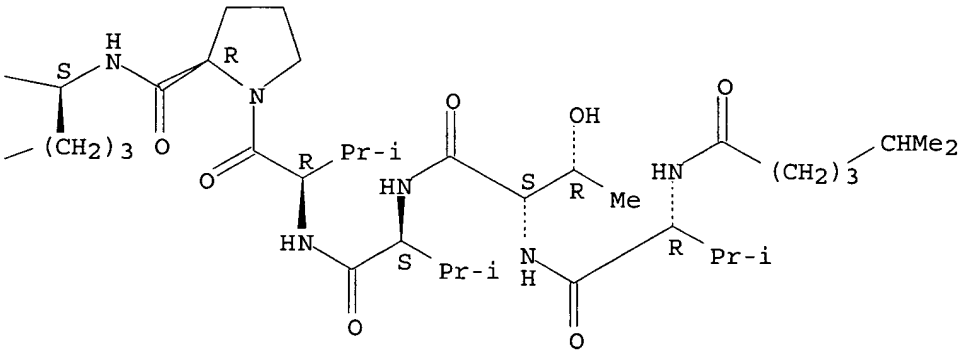
Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



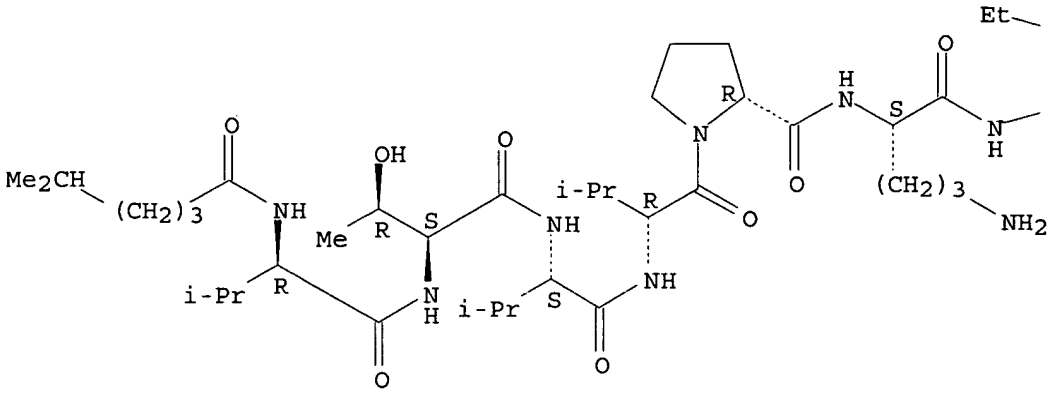
PAGE 1-B



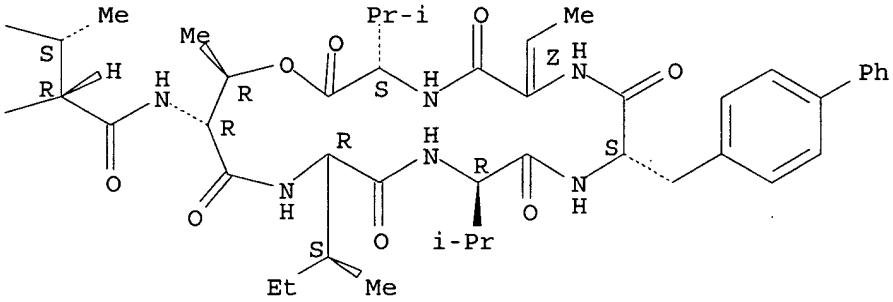
RN 847834-36-0 HCAPLUS
CN Kahalalide F, 11-(3-[1,1'-biphenyl]-4-yl-L-alanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



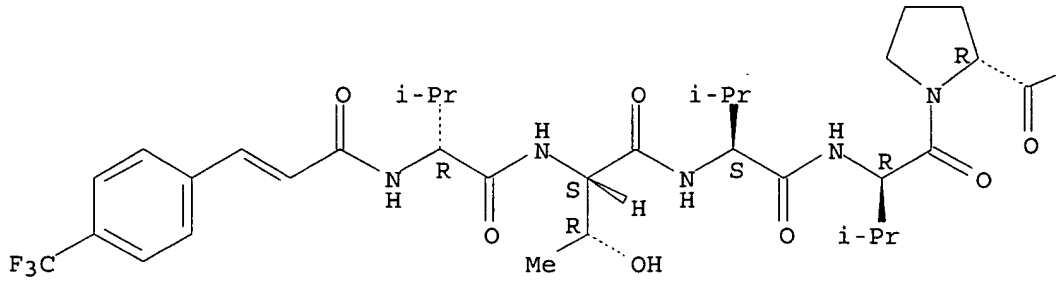
PAGE 1-B



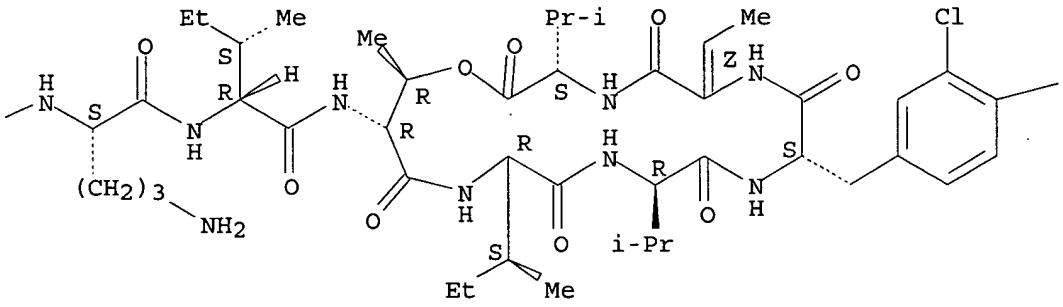
RN 847834-38-2 HCAPLUS
CN Kahalalide F, 1-[N-[1-oxo-3-[4-(trifluoromethyl)phenyl]-2-propenyl]-D-valine]-11-(3,4-dichloro-L-phenylalanine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



PAGE 1-B



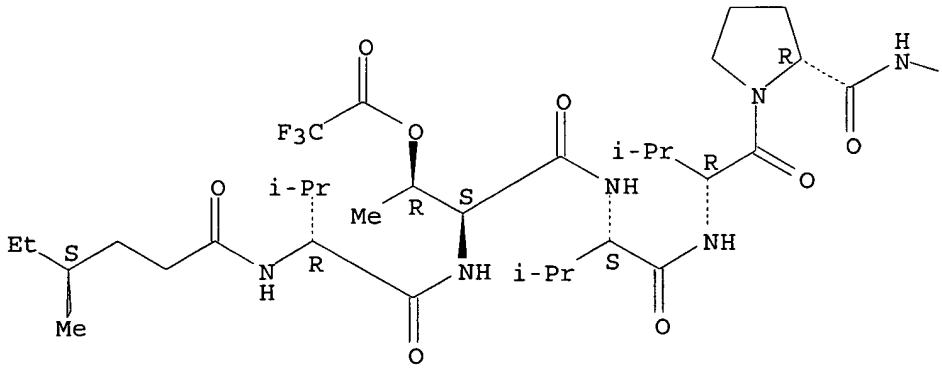
PAGE 1-C

—Cl

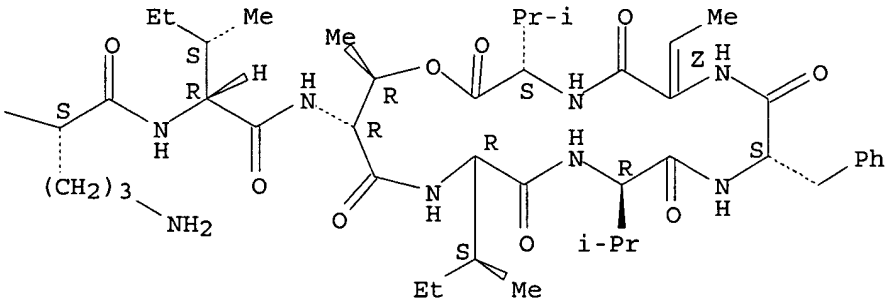
RN 847834-46-2 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]-, trifluoroacetate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



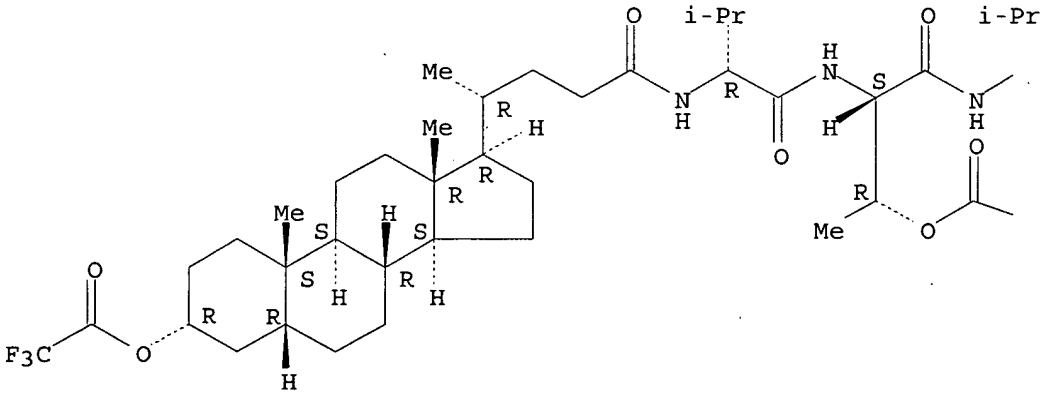
PAGE 1-B



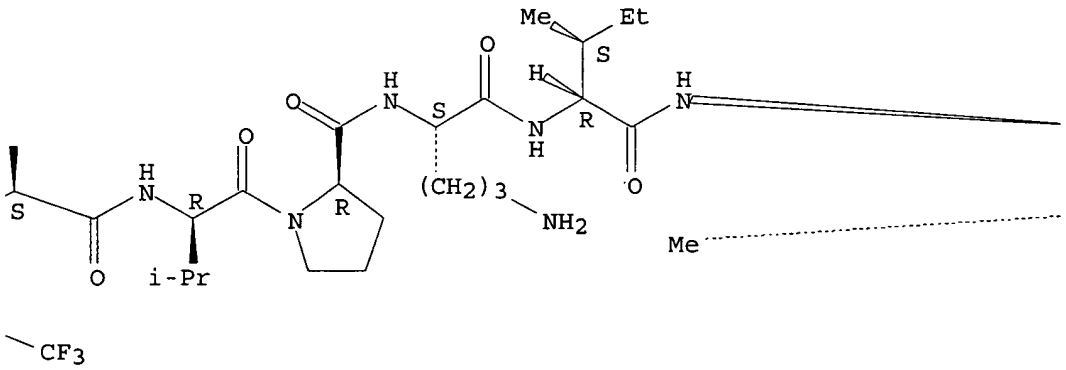
RN 847834-52-0 HCAPLUS
CN Kahalalide F, 1-[N-[(3α,5β)-24-oxo-3-[(trifluoroacetyl)oxy]cholan-24-yl]-D-valine]-, trifluoroacetate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

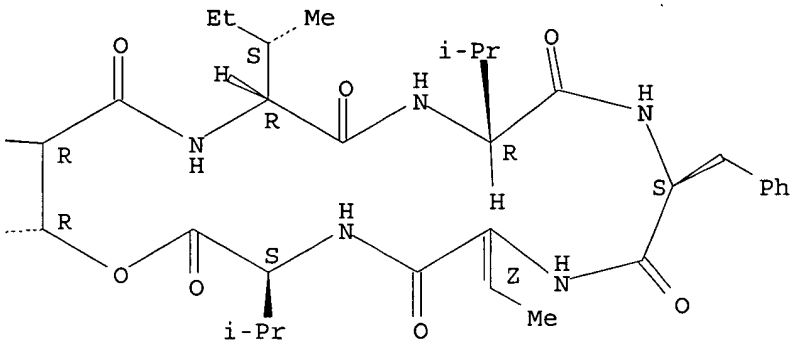
PAGE 1-A



PAGE 1-B



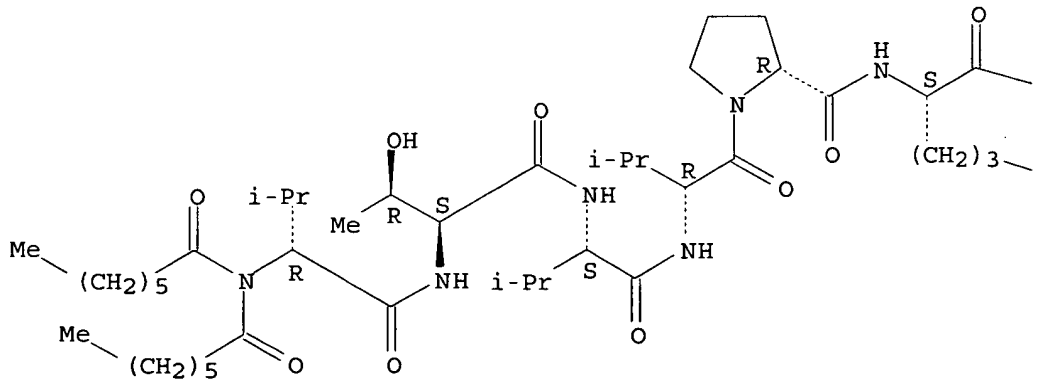
PAGE 1-C



RN 847834-54-2 HCAPLUS
CN Kahalalide F, 1-[N,N-bis(1-oxoheptyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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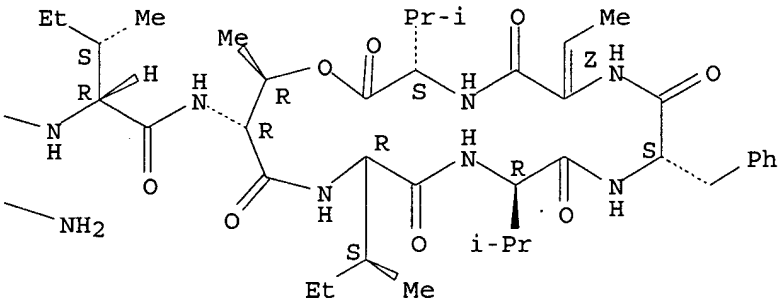
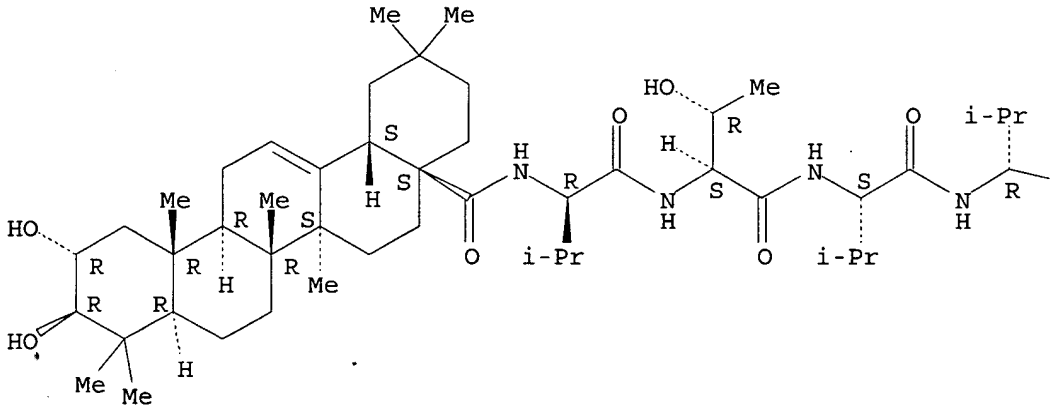


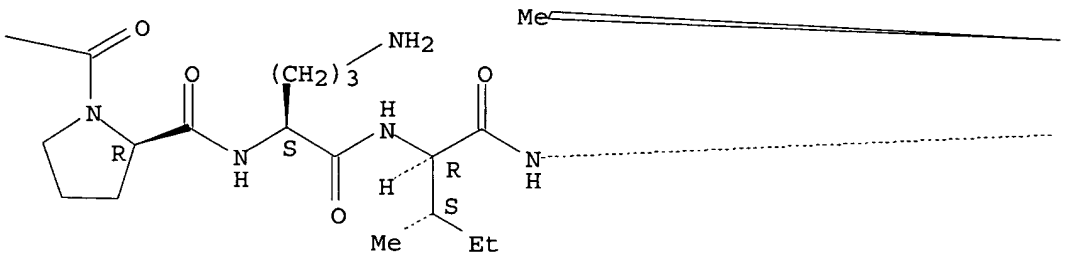
RN 847834-59-7 HCAPLUS
CN Kahalalide F, 1-[N-[(2α,3β)-2,3-dihydroxy-28-oxoolean-12-en-28-yl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



PAGE 1-B



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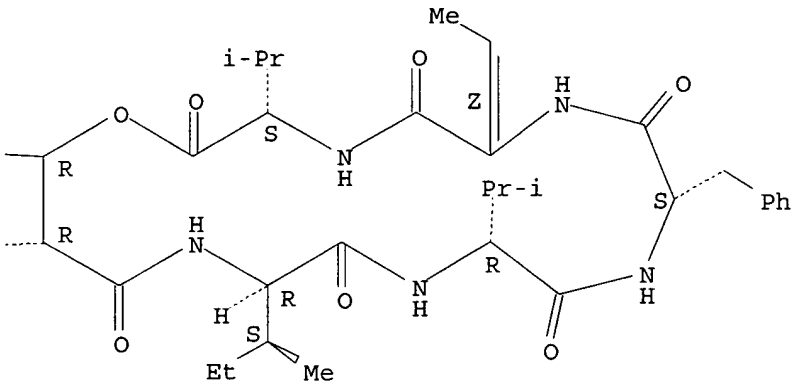
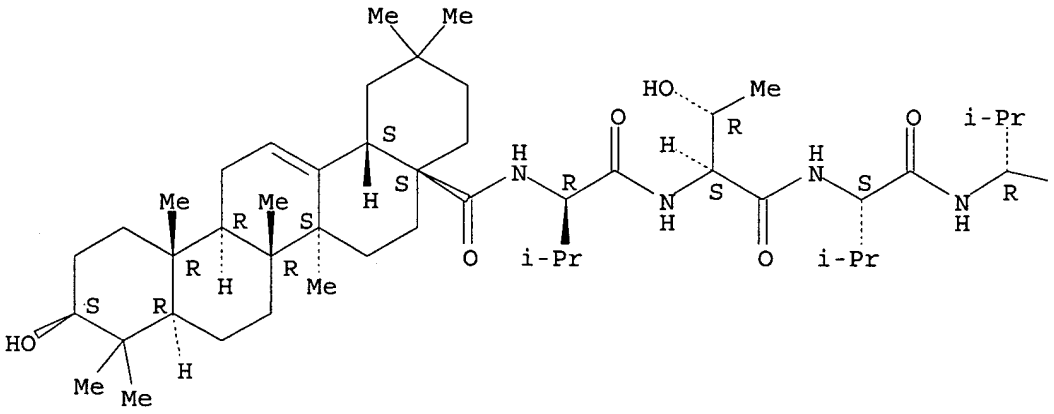


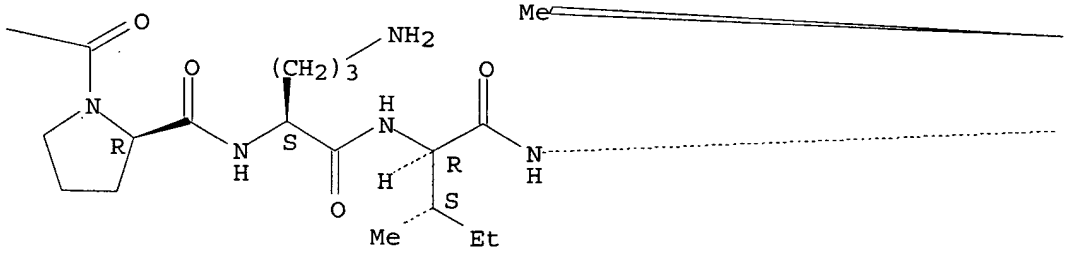
RN 847834-61-1 HCAPLUS
CN Kahalalide F, 1-[N-[(3β)-3-hydroxy-28-oxoolean-12-en-28-yl]-D-valine]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

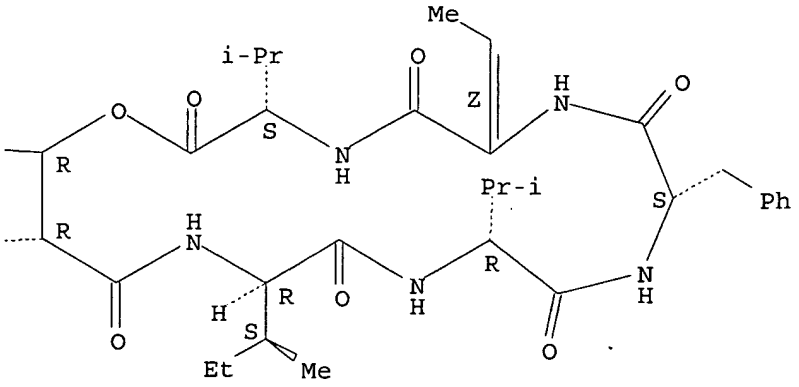
PAGE 1-A



PAGE 1-B



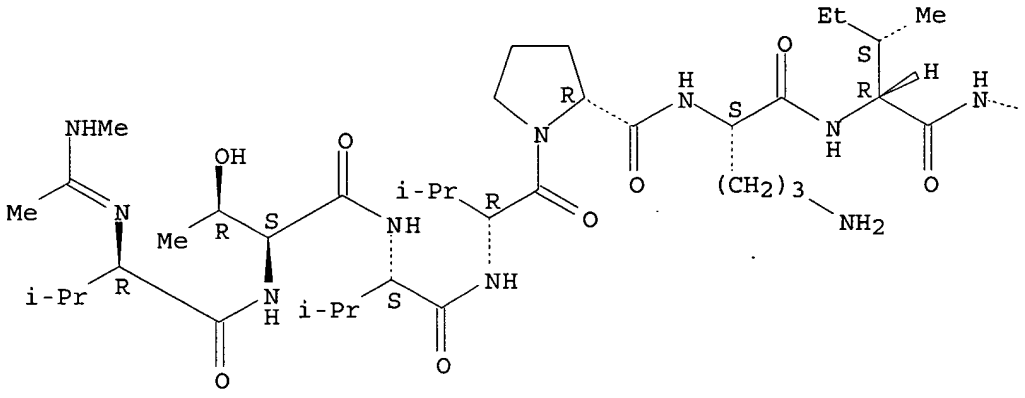
PAGE 1-C



RN 847834-63-3 HCAPLUS
CN Kahalalide F, 1-[N-[1-(methylamino)ethylidene]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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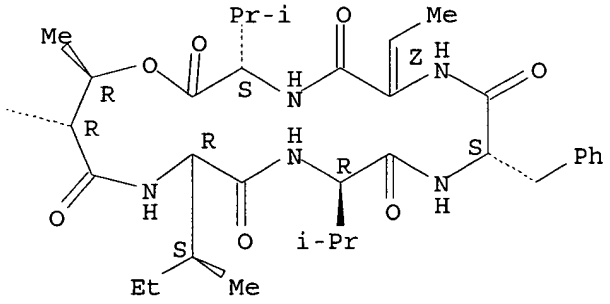
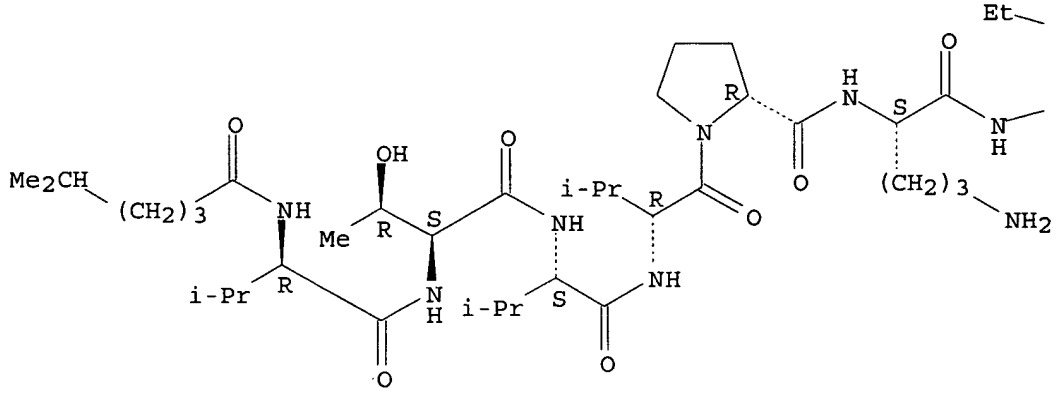


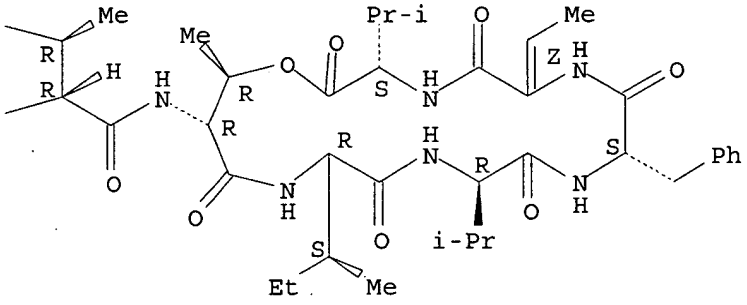
RN 847834-65-5 HCAPLUS
CN Kahalalide F, 7-D-isoleucine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



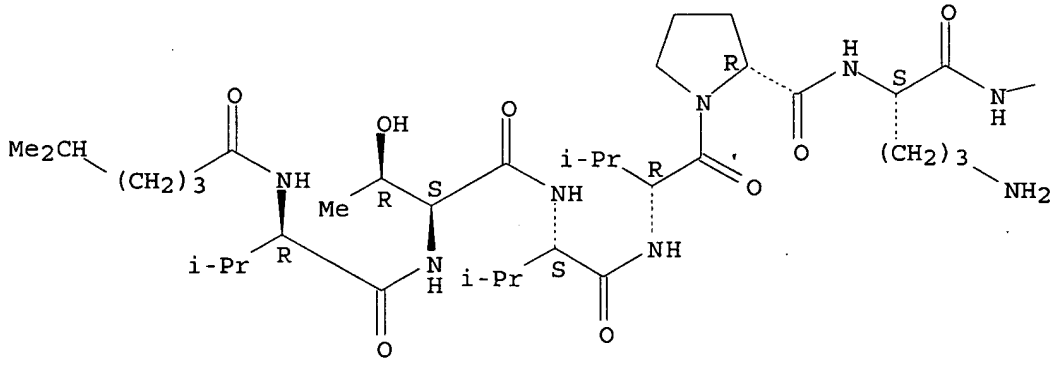
PAGE 1-B



RN 847834-67-7 HCAPLUS
CN Kahalalide F, 7-D-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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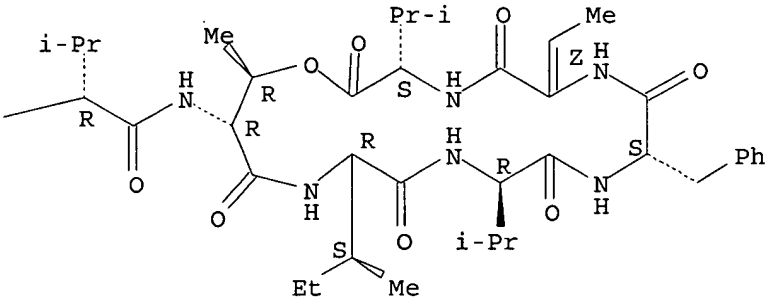
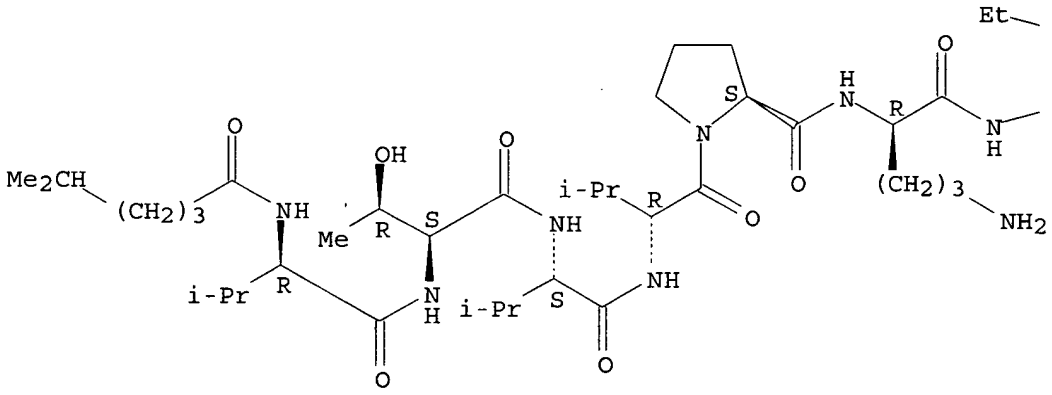


RN 847834-68-8 HCAPLUS
CN Kahalalide F, 5-L-proline-6-D-ornithine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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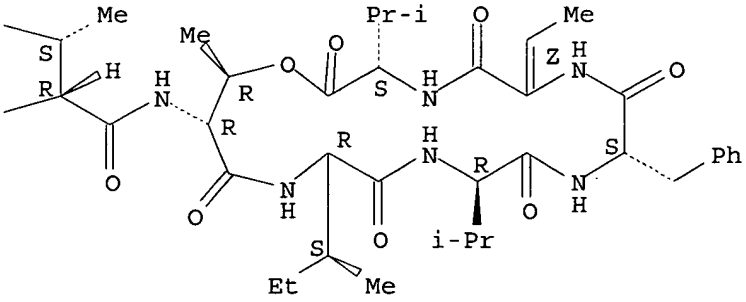
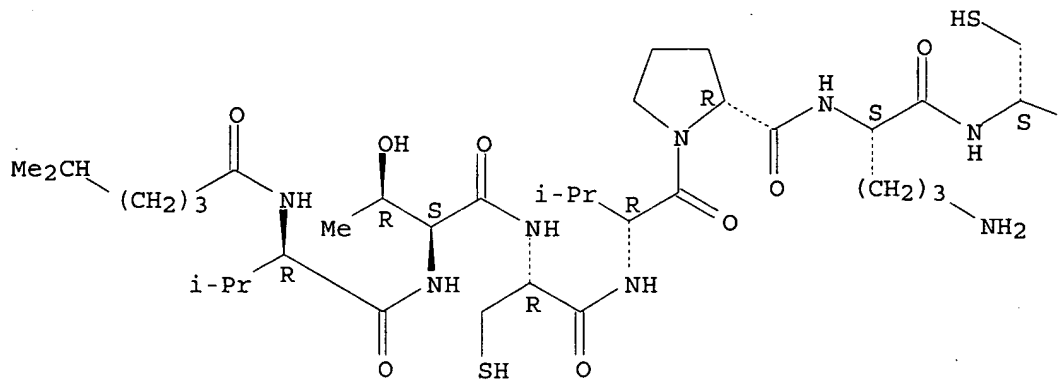


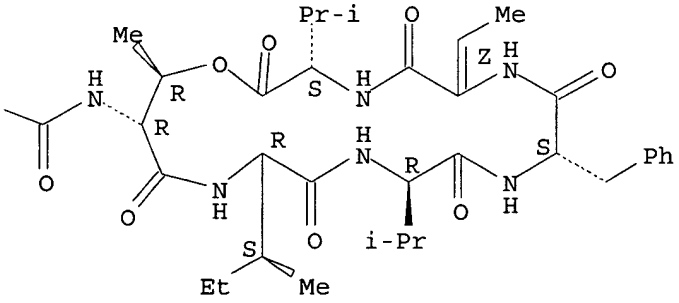
RN 847834-69-9 HCAPLUS
CN L-Valine, N-(5-methyl-1-oxohexyl)-D-valyl-L-threonyl-L-cysteinyl-D-valyl-D-prolyl-L-ornithyl-D-cysteinyl-D-allothreonyl-D-alloisoleucyl-D-valyl-L-phenylalanyl-(2Z)-2-amino-2-butenoyl-, (13→8)-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



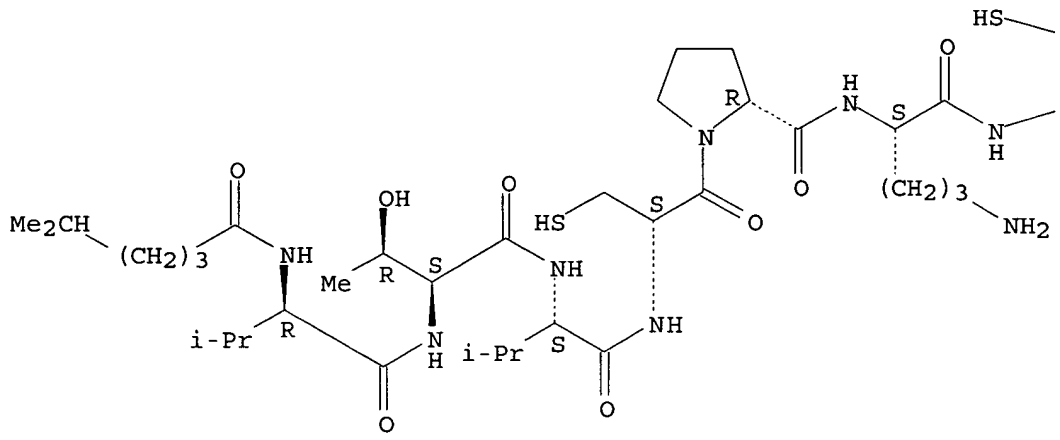
PAGE 1-B



RN 847834-70-2 HCAPLUS
CN L-Valine, N-(5-methyl-1-oxohexyl)-D-valyl-L-threonyl-L-valyl-D-cysteinyl-D-prolyl-L-ornithyl-D-cysteinyl-D-allothreonyl-D-alloisoleucyl-D-valyl-L-phenylalanyl-(2Z)-2-amino-2-butenoyl-, (13→8)-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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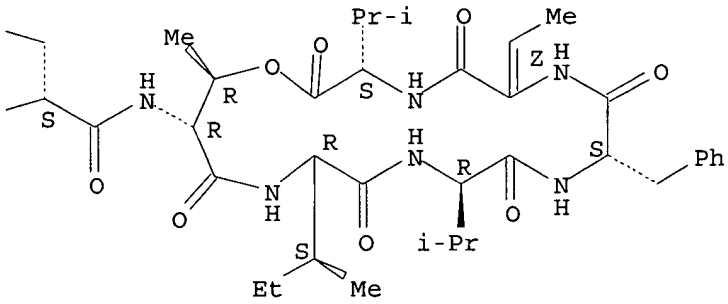
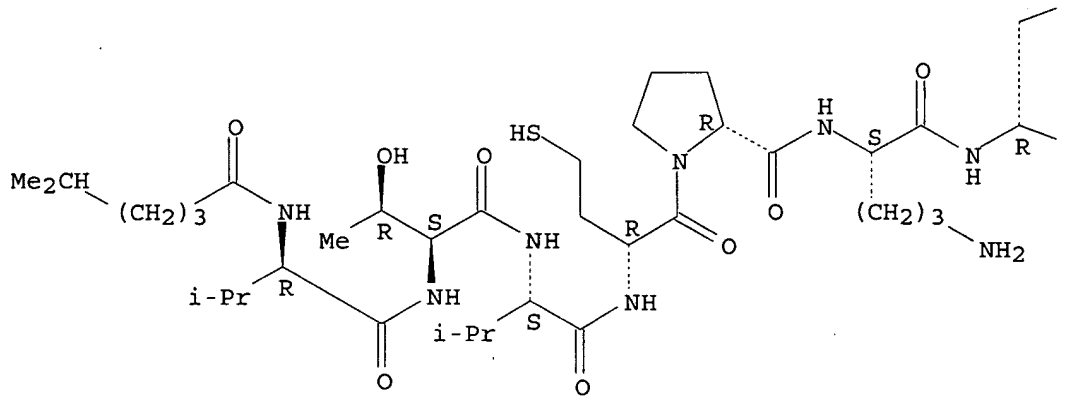


RN 847834-71-3 HCAPLUS
CN L-Valine, N-(5-methyl-1-oxohexyl)-D-valyl-L-threonyl-L-valyl-D-homocysteinyl-D-prolyl-L-ornithyl-D-homocysteinyl-D-allothreonyl-D-alloisoleucyl-D-valyl-L-phenylalanyl-(2Z)-2-amino-2-butenoyl-, (13→8)-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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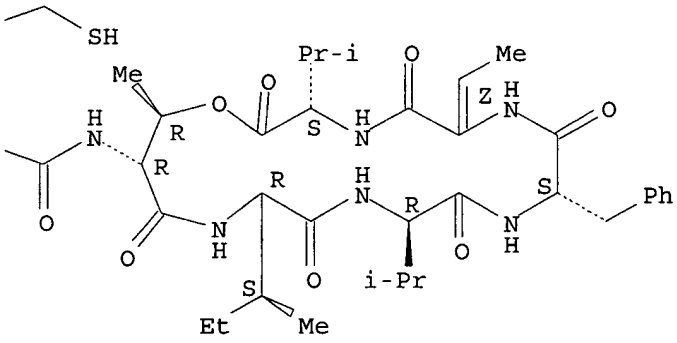
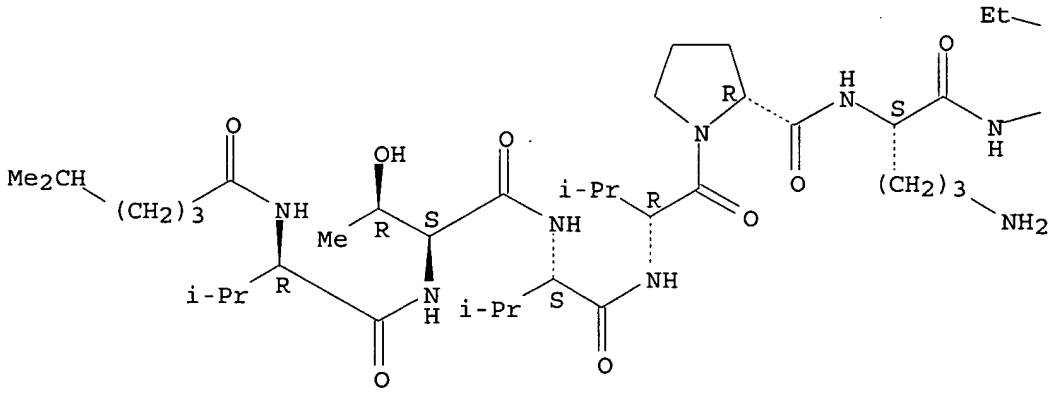


RN 847834-72-4 HCAPLUS
CN Kahalalide F, 13-D-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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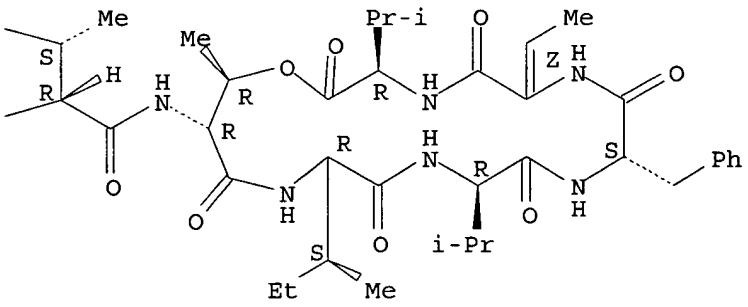
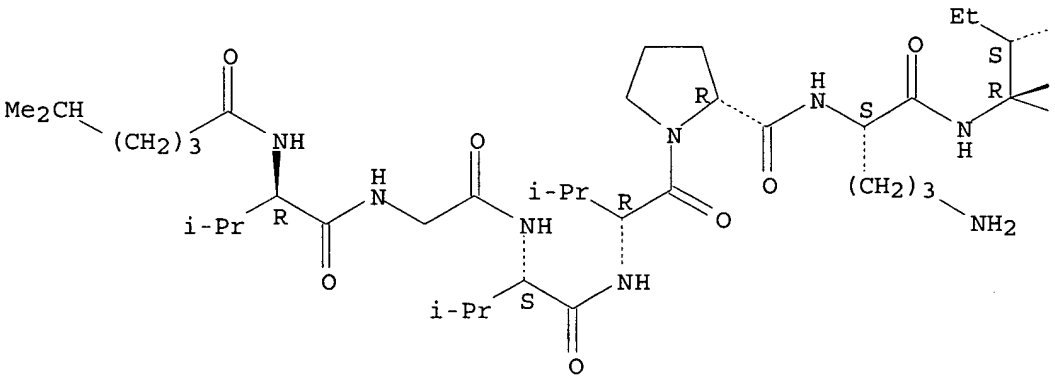


RN 847834-73-5 HCAPLUS
CN Kahalalide F, 2-glycine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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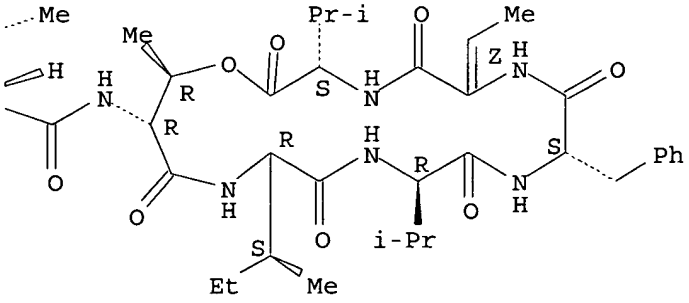
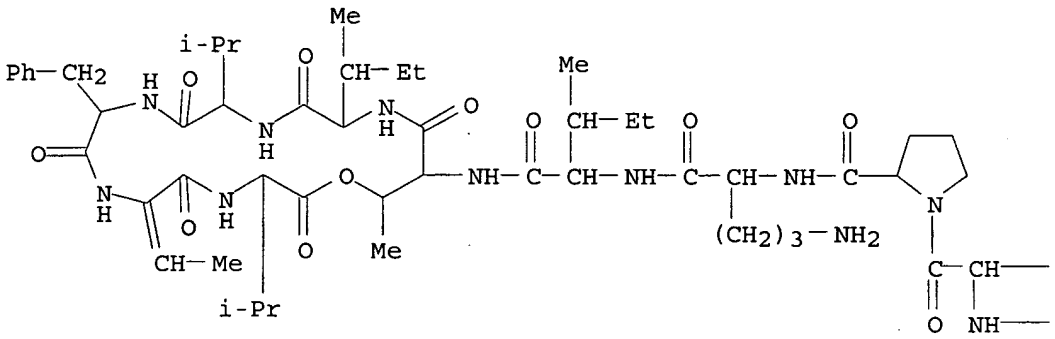


RN 847834-74-6 HCAPLUS
CN Kahalalide F, 2-L-alanine- (9CI) (CA INDEX NAME)

PAGE 1-A



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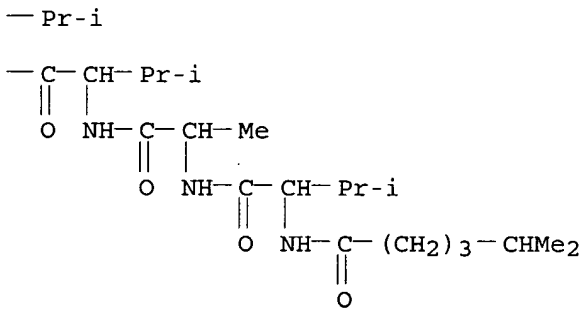
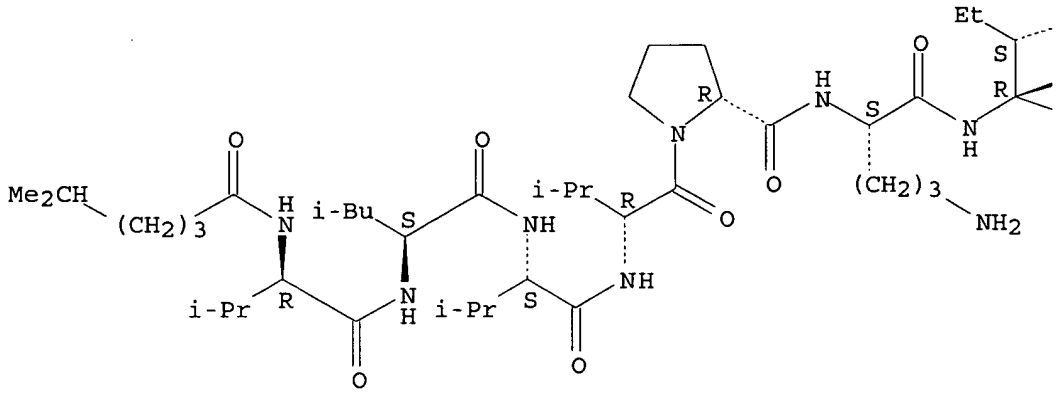


RN 847834-75-7 HCAPLUS
CN Kahalalide F, 2-L-leucine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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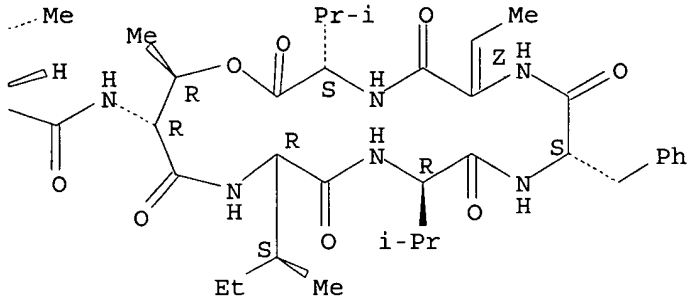
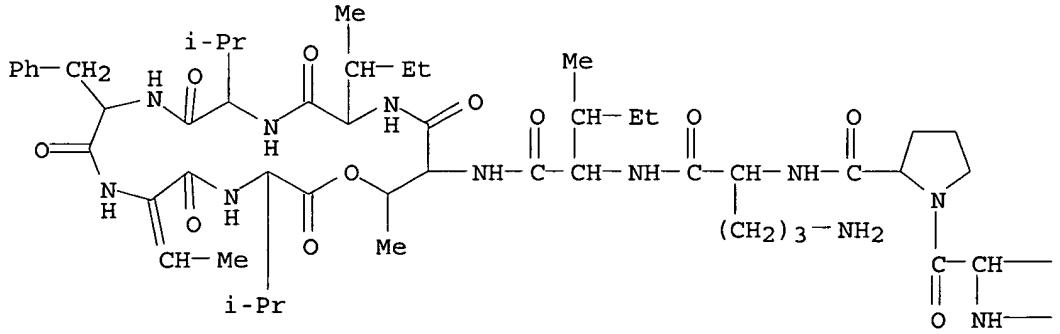
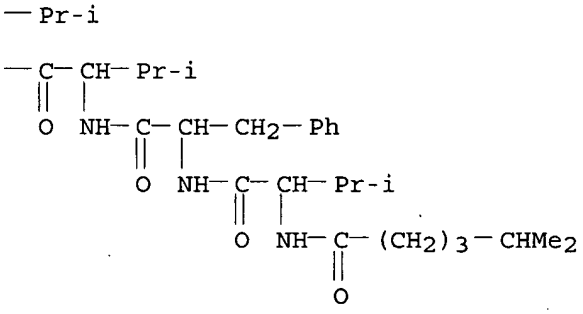


RN 847834-76-8 HCAPLUS
CN Kahalalide F, 2-L-phenylalanine- (9CI) (CA INDEX NAME)

PAGE 1-A



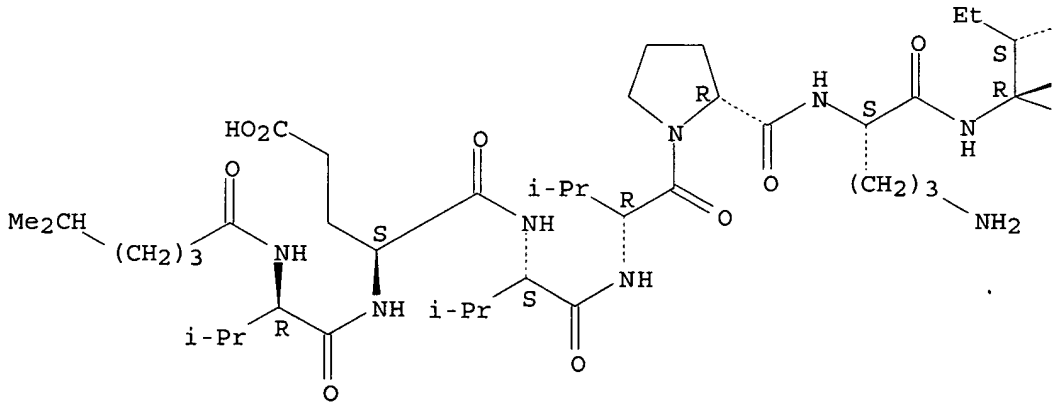
PAGE 1-B



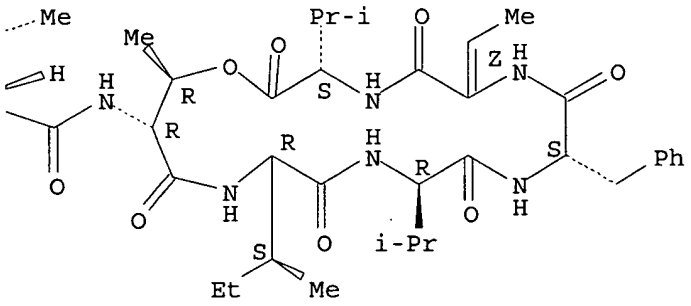
RN 847834-77-9 HCAPLUS
CN Kahalalide F, 2-L-glutamic acid- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



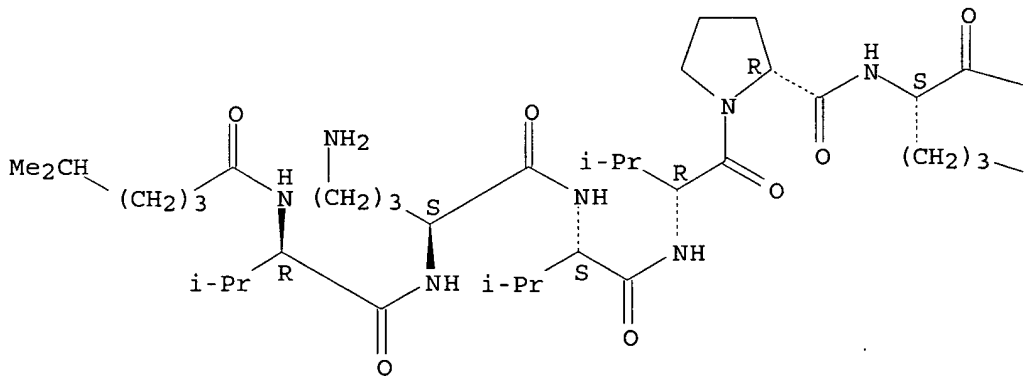
PAGE 1-B



RN 847834-78-0 HCAPLUS
CN Kahalalide F, 2-L-ornithine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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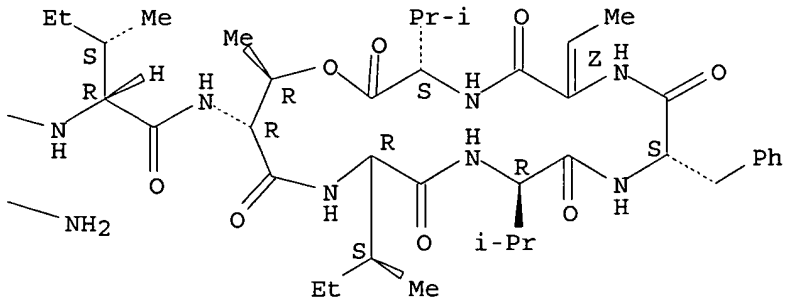
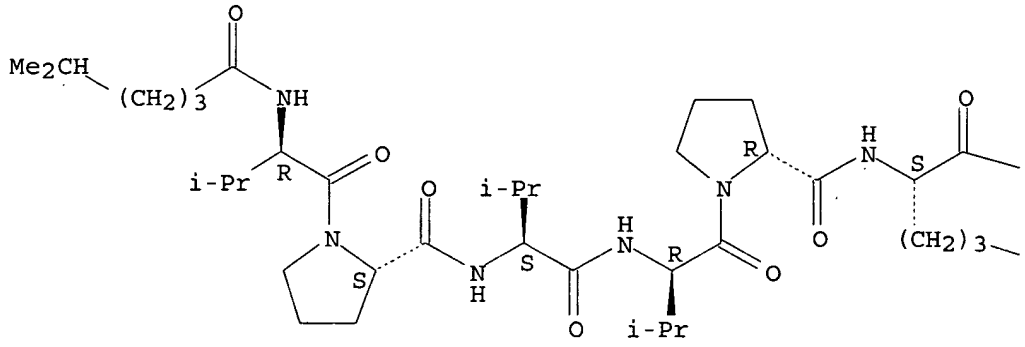


RN 847834-79-1 HCAPLUS
CN Kahalalide F, 2-L-proline- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



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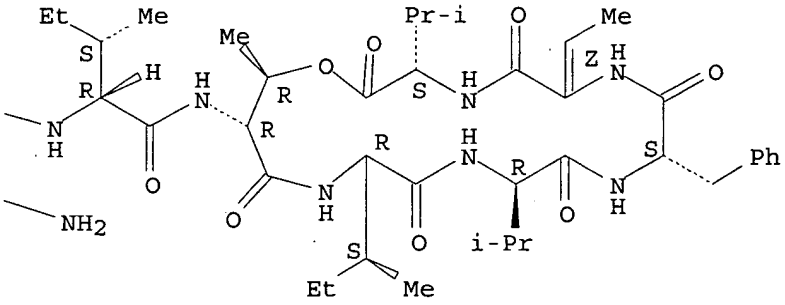
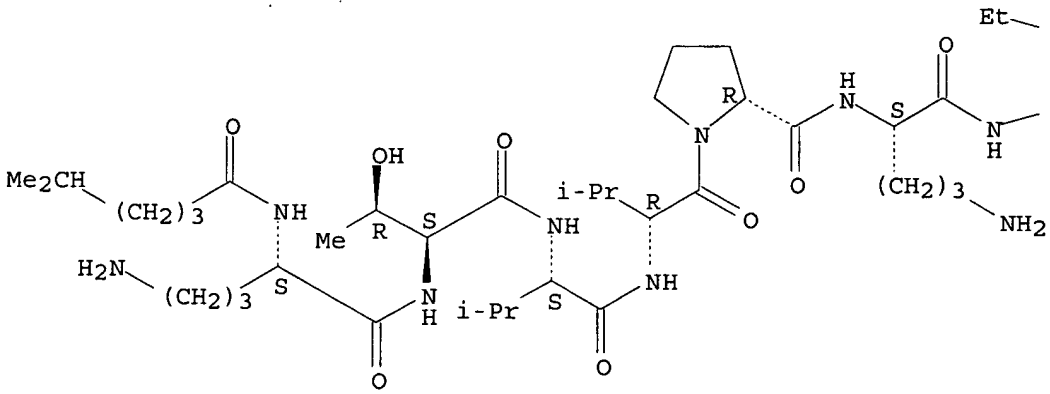


RN 847834-80-4 HCAPLUS
CN Kahalalide F, 1-[N2-(5-methyl-1-oxohexyl)-L-ornithine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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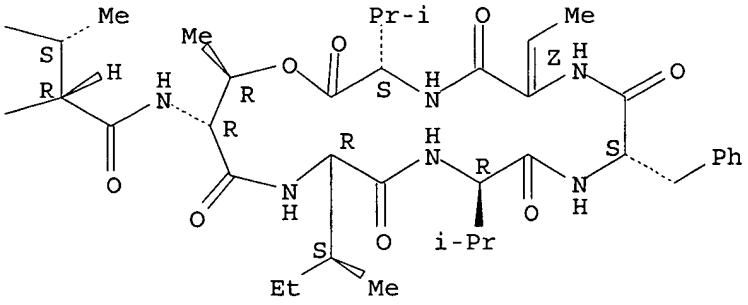
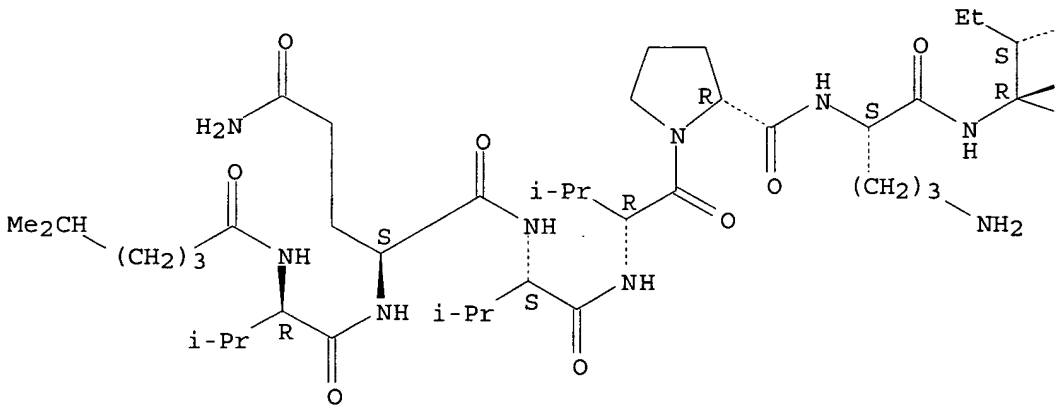


RN 847834-81-5 HCAPLUS
CN Kahalalide F, 2-L-glutamine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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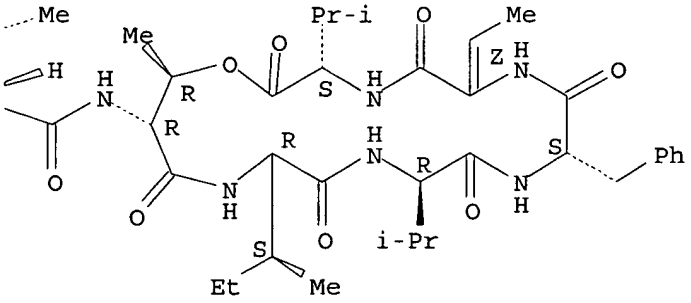
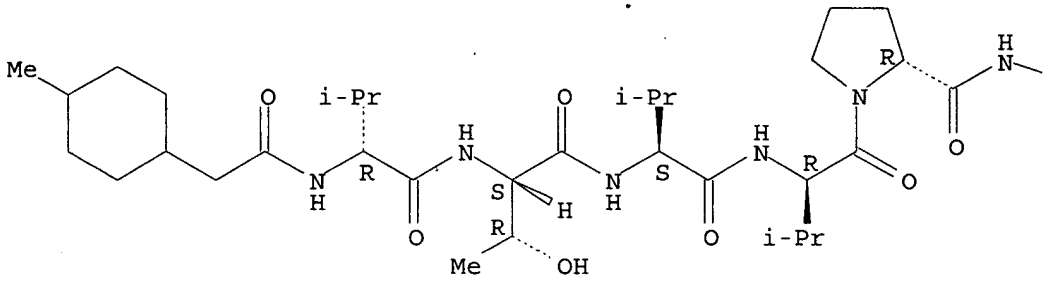


RN 847901-22-8 HCAPLUS

CN Kahalalide F, 1-[N-[(4-methylcyclohexyl)acetyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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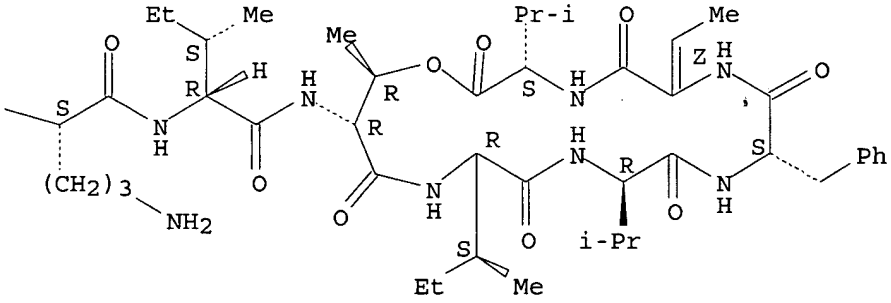
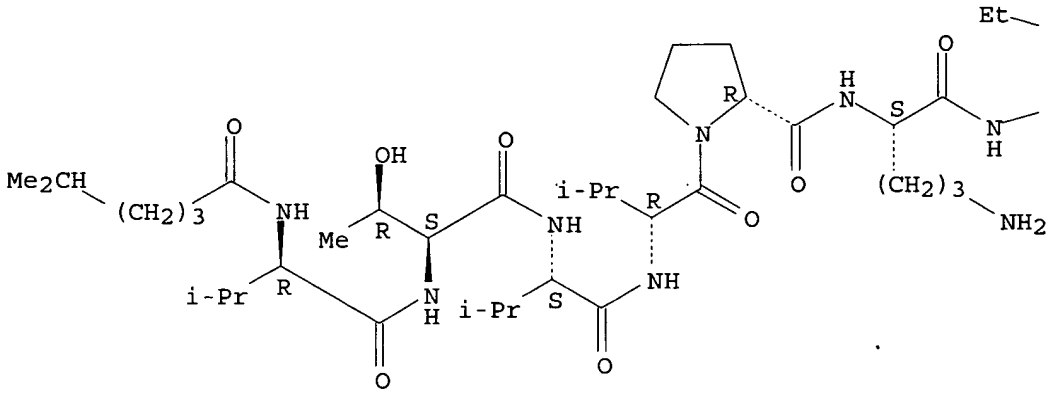


IT 149204-42-2, Kahalalide F
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of kahalalide F analogs as antitumor agents)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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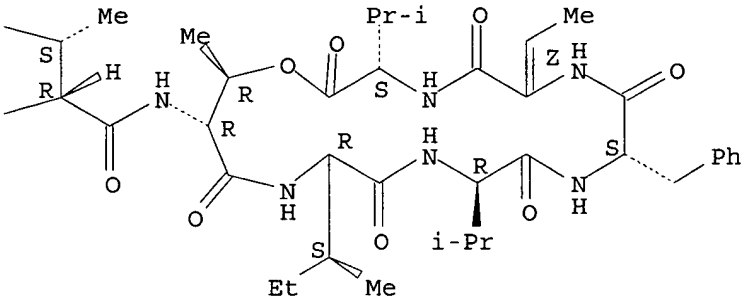


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 17 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:206820 HCAPLUS
DOCUMENT NUMBER: 143:19397
TITLE: Phase I clinical and pharmacokinetic study of kahalalide F in patients with advanced androgen refractory prostate cancer
AUTHOR(S): Rademaker-Lakhai, Jeany M.; Horenblas, Simon; Meinhardt, Willem; Stokvis, Ellen; de Reijke, Theo M.; Jimeno, Jose M.; Lopez-Lazaro, Luis; Lopez Martin, Jose A.; Beijnen, Jos H.; Schellens, Jan H. M.
CORPORATE SOURCE: The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Clinical Cancer Research (2005), 11(5), 1854-1862
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose is to determine the maximum tolerated dose, profile of adverse events,
and dose-limiting toxicity of Kahalalide F (KF) in patients with androgen refractory prostate cancer. Furthermore, the pharmacokinetics after KF administration and preliminary antitumor activity were evaluated. KF is a

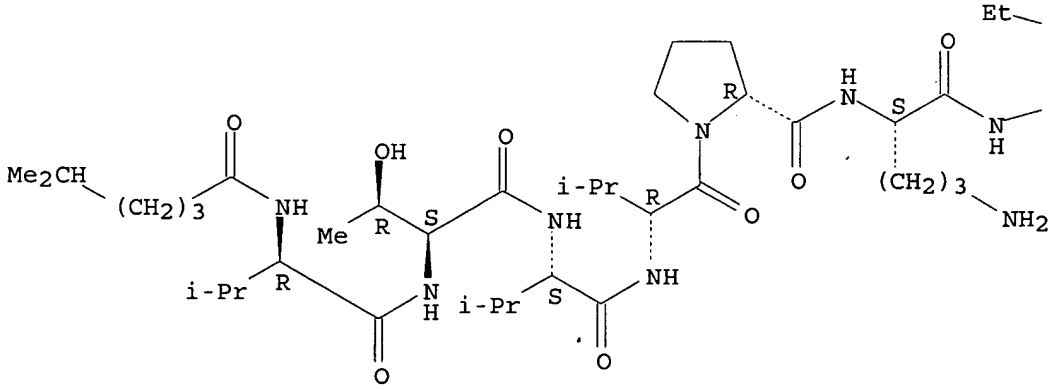
dehydroaminobutyric acid-containing peptide isolated from the marine herbivorous mollusk, Elysia rufescens. Adult patients with advanced or metastatic androgen refractory prostate cancer received KF as an i.v. infusion over 1 h, during five consecutive days every 3 wk. The starting dose was 20 μg per m2 per day. Clin. pharmacokinetics studies were done in all patients using noncompartmental anal. Prostate-specific antigen levels were evaluated as a surrogate marker for activity against prostate cancer. Thirty-two patients were treated at nine dose levels (20-930 μg per m2 per day). The maximum tolerated dose on this schedule was 930 μg per m2 per day. The dose-limiting toxicity was reversible and asymptomatic Common Toxicity Criteria grade 3 and 4 increases in transaminases. The recommended dose for phase II studies is 560 μg per m2 per day. Pharmacokinetics anal. revealed dose linearity up to the recommended dose. Thereafter, a more than proportional increase was observed Elimination was rapid with a mean (SD) terminal half-life (t1/2) of 0.47 h (0.11 h). One patient at dose level 80 μg per m2 per day had a partial response with a prostate-specific antigen decline by at least 50% for ≥4 wk. Five patients showed stable disease. KF can be given safely as a 1-h i.v. infusion during five consecutive days at a dose of 560 μg per m2 per day once every 3 wk.

IT 149204-42-2, Kahalalide F
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase I trial of KF showed MTD to be 930 μg per m2 per day, grade 3, 4 transaminase elevation as DLT and recommended phase II dose to be 560 μg per m2 per day for patient with advanced androgen refractory prostate cancer)

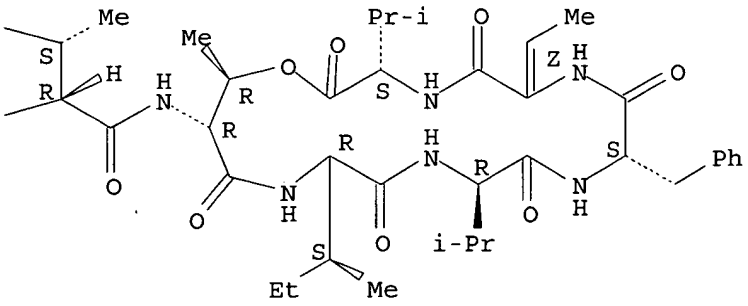
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

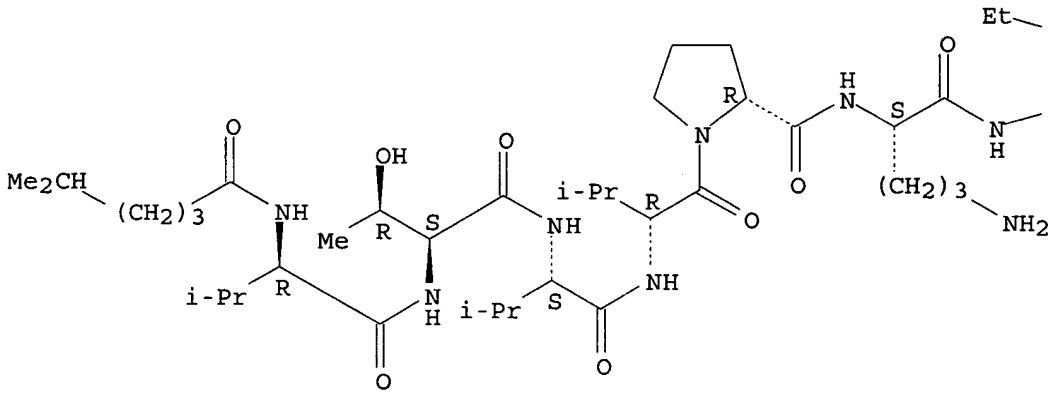
L12 ANSWER 18 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:144032 HCAPLUS
DOCUMENT NUMBER: 142:388504
TITLE: Stable isotopically labeled internal standards in quantitative bioanalysis using liquid chromatography/mass spectrometry: necessity or not?
AUTHOR(S): Stokvis, Ellen; Rosing, Hilde; Beijnen, Jos H.
CORPORATE SOURCE: Department of Pharmacy & Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Rapid Communications in Mass Spectrometry (2005), 19(3), 401-407
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It appears to be a general belief that stable isotopically labeled (SIL) internal stds. yield better assay performance results for quant. bioanal. liquid chromatog./mass spectrometry (LC/MS) assays than does any other internal standard In this article we describe our experiences with structural analogs and SIL internal stds. and their merits and demerits. SIL internal stds. are the first choice, but deuterium-labeled compds. may demonstrate unexpected behavior, such as different retention times or recoveries, than the analyte. In addition, a SIL internal standard with identical chemical properties as the analyte may cover up assay problems with stability, recovery, and ion suppression. Since SIL internal stds. are not always available or are very expensive, structural analogs can be used, however, with consideration of several issues, which are usually displayed during method validation.

IT 149204-42-2, Kahalalide F
RL: ANT (Analyte); ANST (Analytical study)
(stable isotopically labeled internal stds. in quant. bioanal. using liquid chromatog./mass spectrometry)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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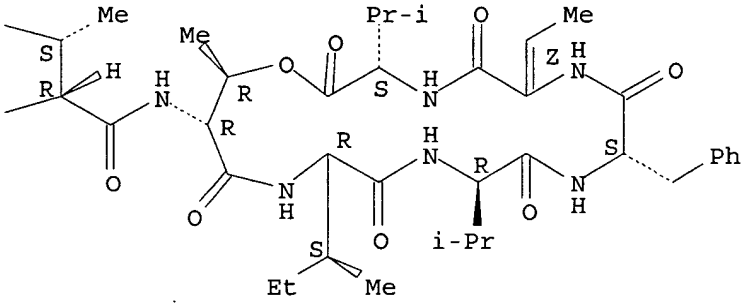
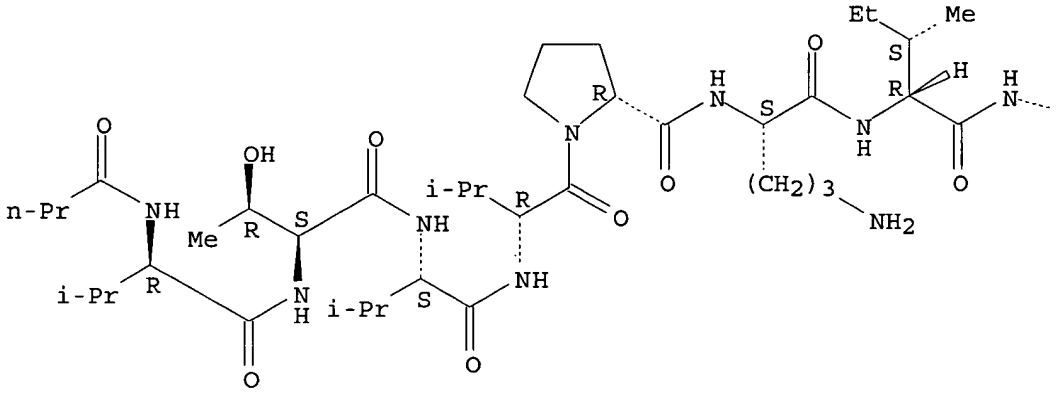


IT 353491-55-1 782486-09-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stable isotopically labeled internal stds. in quant. bioanal. using liquid chromatog./mass spectrometry)
RN 353491-55-1 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxobutyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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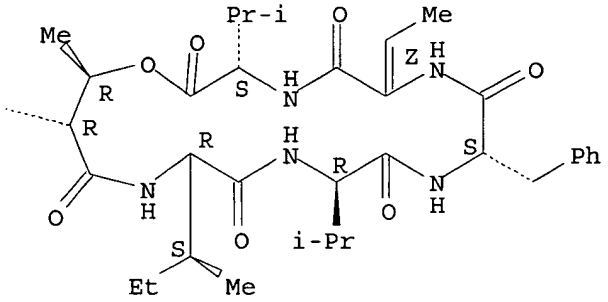
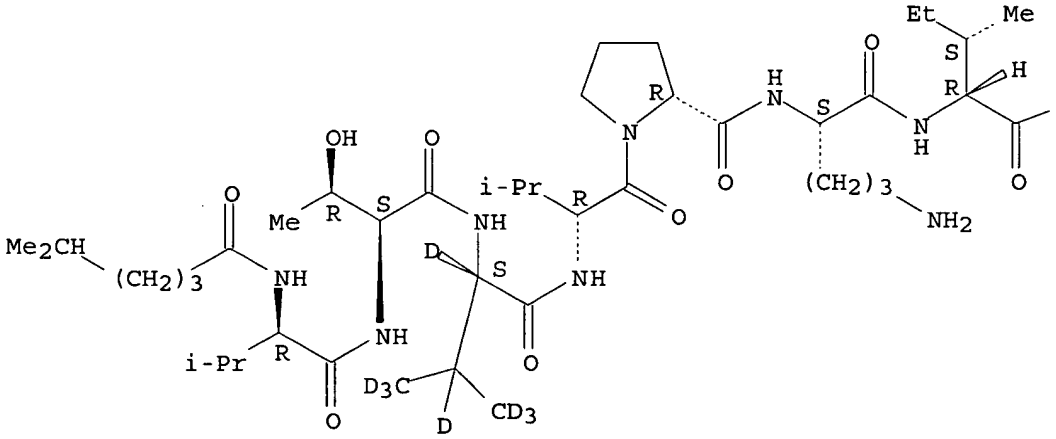


RN 782486-09-3 HCAPLUS
CN Kahalalide F, 3-(L-valine-2,3,4,4,4,4',4',4'-d8)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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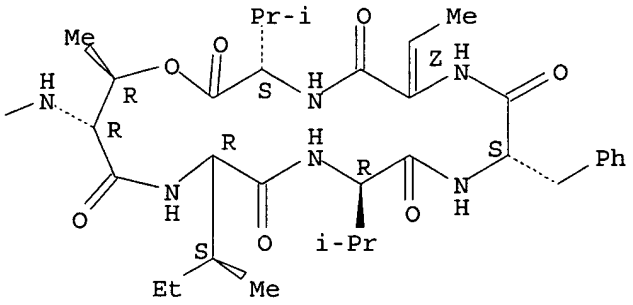
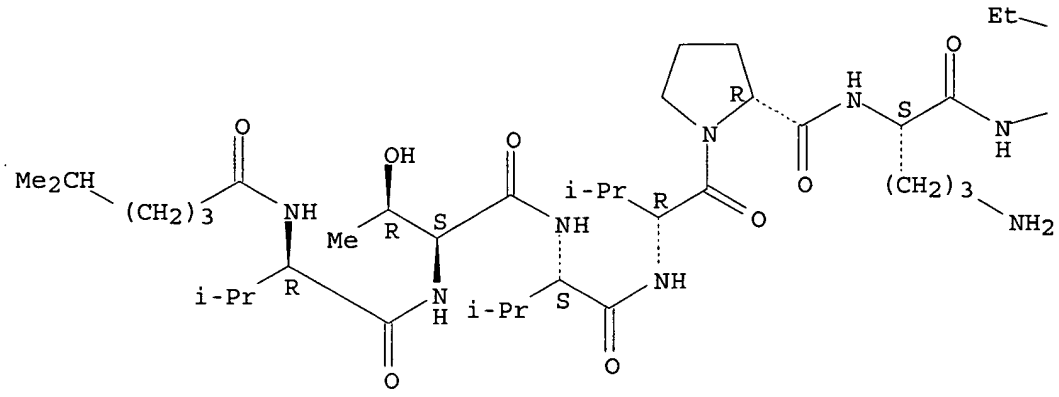


REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

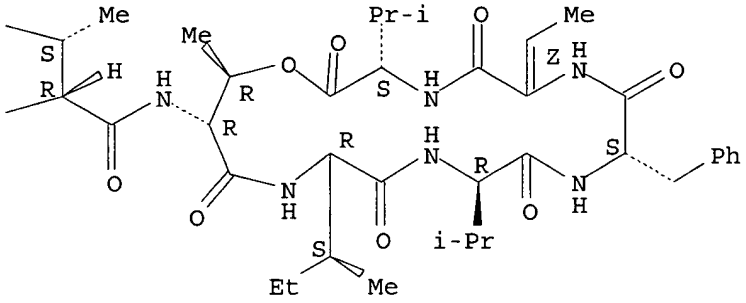
L12 ANSWER 19 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:136757 HCAPLUS
DOCUMENT NUMBER: 143:318056
TITLE: Applications of products from marine organisms
AUTHOR(S): Nuijen, B.; den Brok, M. W. J.; Manada, C.; Bult, A.; Beijnen, J. H.
CORPORATE SOURCE: Nederlands Kankerinstituut, Amsterdam, Neth.
SOURCE: Pharmaceutisch Weekblad (2005), 140(3), 104-109
CODEN: PHWEAW; ISSN: 0031-6911
PUBLISHER: Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Dutch
AB A review of antitumor agents derived from marine organisms. The drugs aplidine (from Aplidium albicans), kahalalide F (from Elysia rufescens), and ES-285 (from Spisula polynyma) are examined in detail.
IT 149204-42-2, Kahalalide F
RL: NPO (Natural product occurrence); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(antitumor applications of products from marine organisms)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



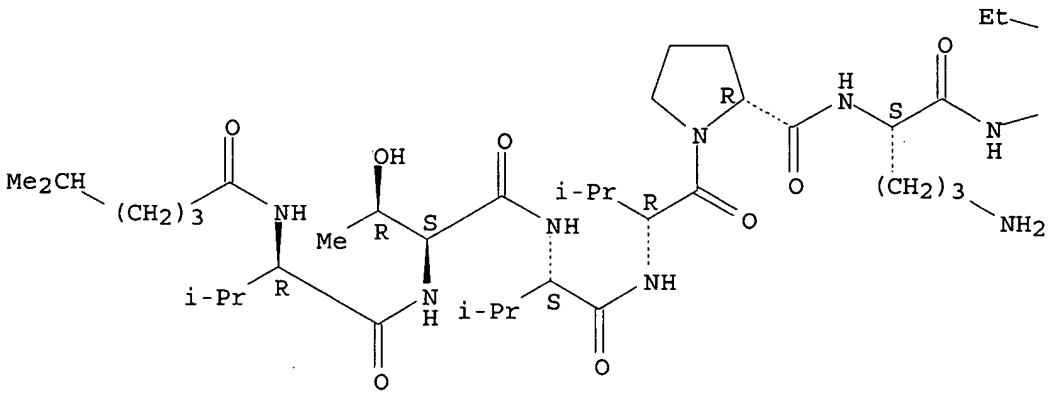
PAGE 1-B



L12 ANSWER 20 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:95095 HCAPLUS
DOCUMENT NUMBER: 143:52574
TITLE: Technology evaluation: Kahalalide F, PharmaMar
AUTHOR(S): Hamann, Mark T.
CORPORATE SOURCE: The School of Pharmacy and Department of Chemistry and Biochemistry, University of Mississippi, MS, 38677, USA
SOURCE: Current Opinion in Molecular Therapeutics (2004), 6(6), 657-665
CODEN: CUOTFO; ISSN: 1464-8431
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Kahalalide F is a depsipeptide under development by PharmaMar as a potential treatment for solid tumors. It is currently undergoing phase II clin. trials.
IT 149204-42-2, Kahalalide F
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase II clin. trial of kahalalide F showed anticancer activity against solid tumors in human)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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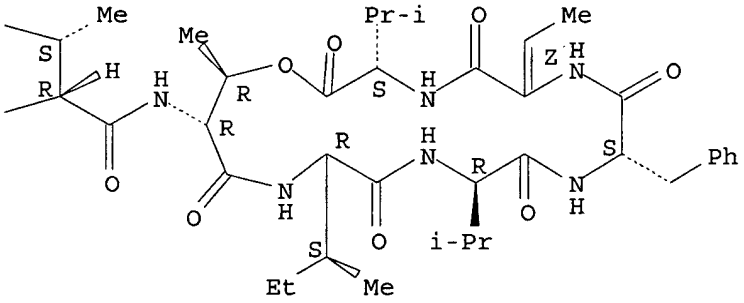


REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 21 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:34709 HCAPLUS
DOCUMENT NUMBER: 142:100283
TITLE: Combination of hemocyanin from spiders with dolastatine form Dolabella for the treatment of prostate cancer
INVENTOR(S): Weickmann, Dirk
PATENT ASSIGNEE(S): Toximed G.m.b.H., Germany
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005002494	A2	20050113	WO 2004-DE1386	20040701
WO 2005002494	A3	20050224		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10329847 A1 20050120 DE 2003-10329847 20030702
PRIORITY APPLN. INFO.: DE 2003-10329847 A 20030702

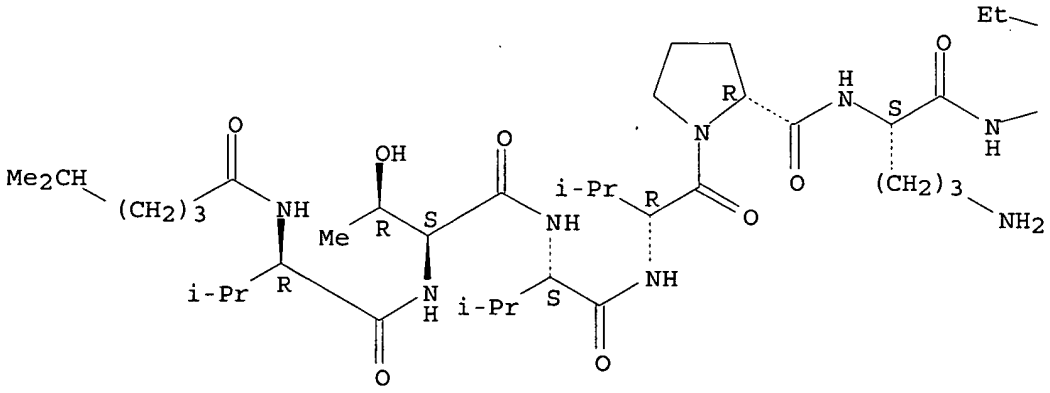
AB The invention concerns a combination of (a) hemocyanin from the hemolymphs of certain bird-eating spiders; (b) substances that are antagonists, synergists, and penetration enhancers to hemocyanin and that are obtained from the fractionation of spider venoms; (c) dolastatine form Dolabella auricularia or a preparation named Kahalalide F from Elysia rufescens. Hemocyanine, antagonists, synergists, and penetration enhancers are isolated by various chromatog. methods; the fractions or their mixts. are lyophilized for storage. For formulation, isotonic solution, buffer, albumin, glutamine, antimicrobial agent, etc. are added.

IT 149204-42-2P, Kahalalide F
RL: NPO (Natural product occurrence); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(combination of hemocyanin from spiders with dolastatine form Dolabella for treatment of prostate cancer)

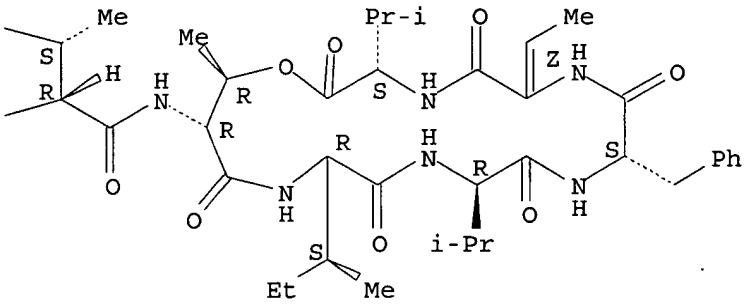
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 22 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:740175 HCAPLUS
DOCUMENT NUMBER: 141:236712
TITLE: Use of kahalalide compounds for the manufacture of a medicament for the treatment of psoriasis
INVENTOR(S): Izquierdo Delso, Miguel Angel
PATENT ASSIGNEE(S): Pharma Mar, S.A.U., Spain; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004075910	A1	20040910	WO 2004-GB757	20040226
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004216443	A1	20040910	AU 2004-216443	20040226
CA 2516458	AA	20040910	CA 2004-2516458	20040226
EP 1596879	A1	20051123	EP 2004-714847	20040226
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: GB 2003-4367 A 20030226
WO 2004-GB757 W 20040226

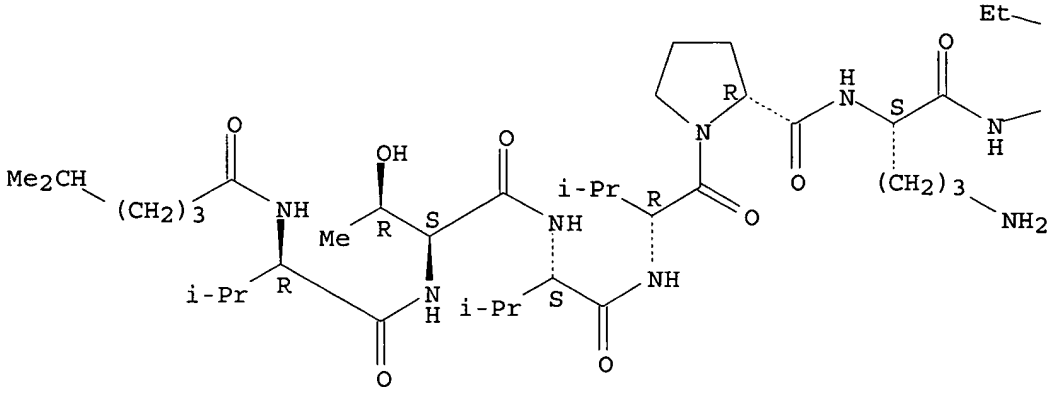
AB Kahalalide compds., in particular kahalalide F, are of use in a method to treat a mammal suffering from skin disease with avoiding toxicity and leading to clin. improvement.

IT 149204-42-2, Kahalalide f
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kahalalide compds. for the treatment of psoriasis)

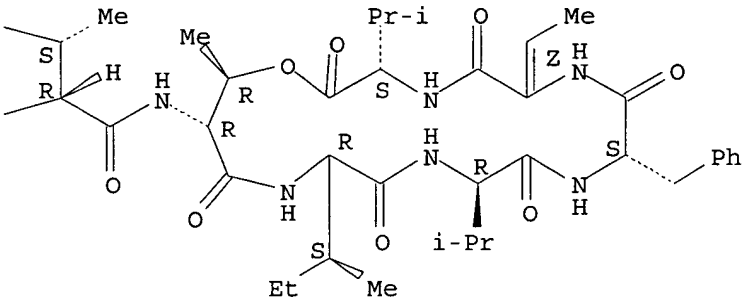
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



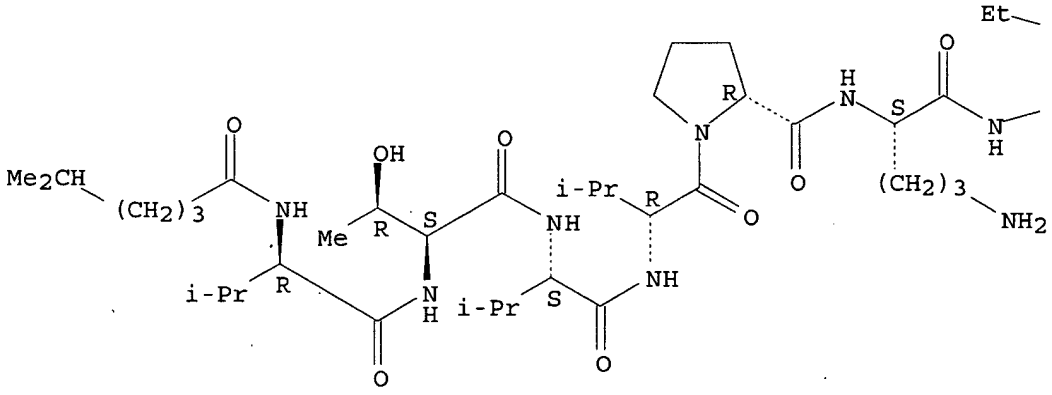
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 23 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:654292 HCAPLUS
DOCUMENT NUMBER: 141:374378
TITLE: Switching from an analogous to a stable isotopically labeled internal standard for the LC-MS/MS quantitation of the novel anticancer drug Kahalalide F significantly improves assay performance
AUTHOR(S): Stokvis, E.; Rosing, H.; Lopez-Lazaro, L.; Schellens, J. H. M.; Beijnen, J. H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Slotervaart Hospital, Amsterdam, 1066 EC, Neth.
SOURCE: Biomedical Chromatography (2004), 18(6), 400-402
CODEN: BICHE2; ISSN: 0269-3879
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The importance of a stable isotopically labeled (SIL) internal standard for the quant. LC-MS/MS assay for Kahalalide F in human plasma is highlighted. Similar results can be expected for other LC-MS/MS assays. Therefore, we emphasize the need for an SIL internal standard for accurate and precise LC-MS/MS assays of drugs in biol. matrixes.

IT 149204-42-2, Kahalalide F
RL: ANT (Analyte); ANST (Analytical study)
(switching from an analogous to a stable isotopically labeled internal standard for the LC-MS/MS quantitation of the novel anticancer drug Kahalalide F significantly improves assay performance)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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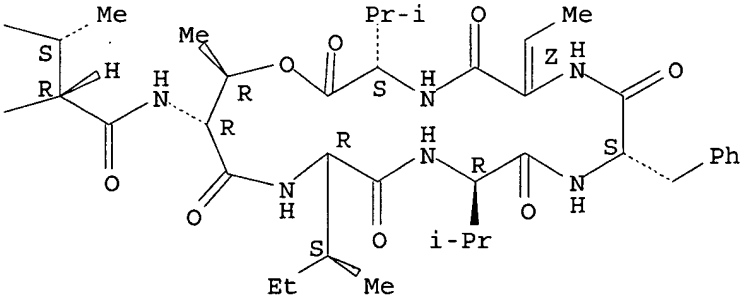
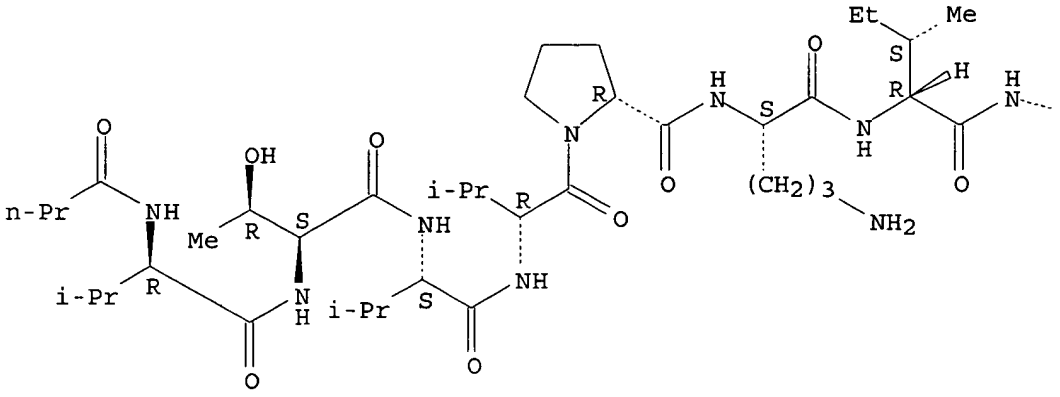


IT 353491-55-1 782486-09-3
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(switching from an analogous to a stable isotopically labeled internal standard for the LC-MS/MS quantitation of the novel anticancer drug Kahalalide F significantly improves assay performance)
RN 353491-55-1 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxobutyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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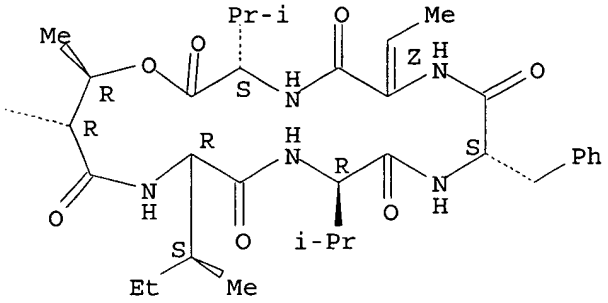
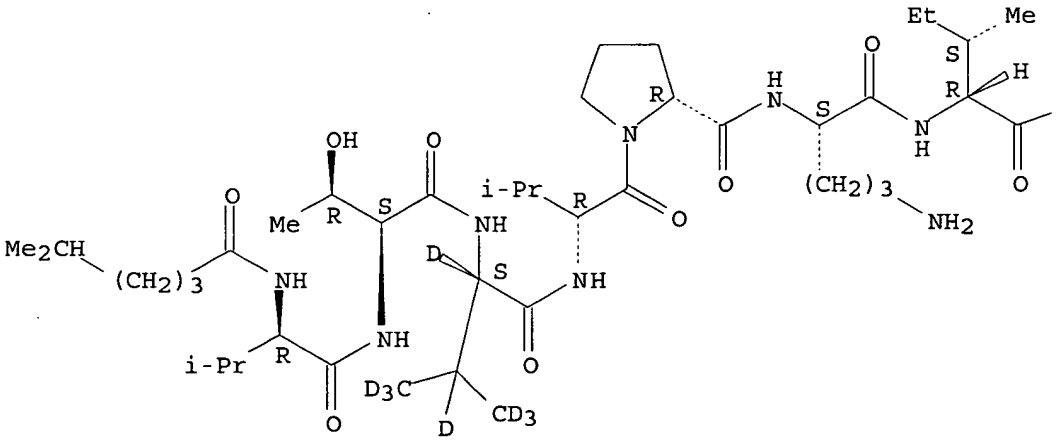


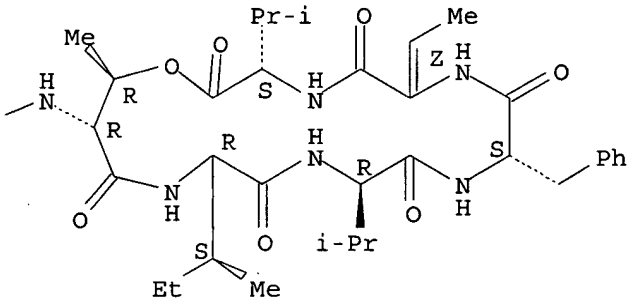
RN 782486-09-3 HCAPLUS
CN Kahalalide F, 3-(L-valine-2,3,4,4,4,4',4',4'-d8)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 24 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:354967 HCAPLUS
DOCUMENT NUMBER: 140:357671
TITLE: Preparation of kahalalide antitumoral compounds
INVENTOR(S): Faircloth, Glynn Thomas; Elices, Mariano; Sasak, Halina; Aviles Marin, Pablo Manuel; Cuevas Marchante, Maria Del Carmen
PATENT ASSIGNEE(S): Pharma Mar, S.A.U., Spain
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035613	A2	20040429	WO 2003-US33207	20031020
WO 2004035613	A3	20040729		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003033012	A1	20030424	WO 2002-GB4735	20021018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

CA 2501089	AA	20040429	CA 2003-2501089		20031020
AU 2003285911	A1	20040504	AU 2003-285911		20031020
BR 2003015489	A	20050823	BR 2003-15489		20031020
EP 1572726	A2	20050914	EP 2003-779140		20031020
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006517195	T2	20060720	JP 2005-501483		20031020
NO 2005002379	A	20050715	NO 2005-2379		20050513
PRIORITY APPLN. INFO.:			WO 2002-GB4735	A	20021018
			GB 2003-4367	A	20030226
			GB 2003-14725	A	20030624
			US 2001-348449P	P	20011019
			WO 2001-GB4821	A	20011031
			GB 2002-22409	A	20020926
			WO 2003-US33207	W	20031020

AB The invention is directed to new kahalalide antitumoral compds., in particular to analogs of kahalalide F, which are useful as antitumoral, antiviral and antifungal agents and in the treatment of psoriasis. Thus, kahalalide F analogs in which the 5-methylhexanoc acid residue has been replaced by (S)- and (R)-4-methylhexanoic acid were prepared and assayed for cytotoxic activity against various cell lines.

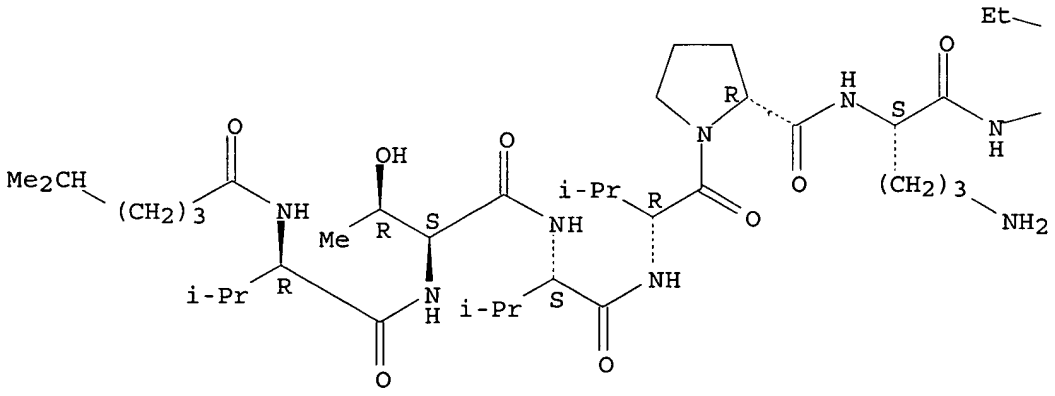
IT 149204-42-2DP, Kahalalide f, analogs 681272-30-0P
681272-31-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of kahalalide antitumoral compds.)

RN 149204-42-2 HCAPLUS

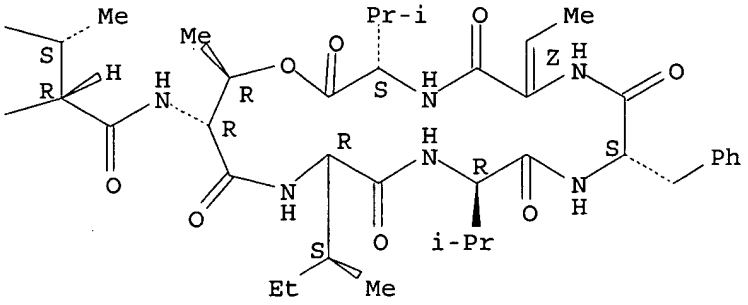
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



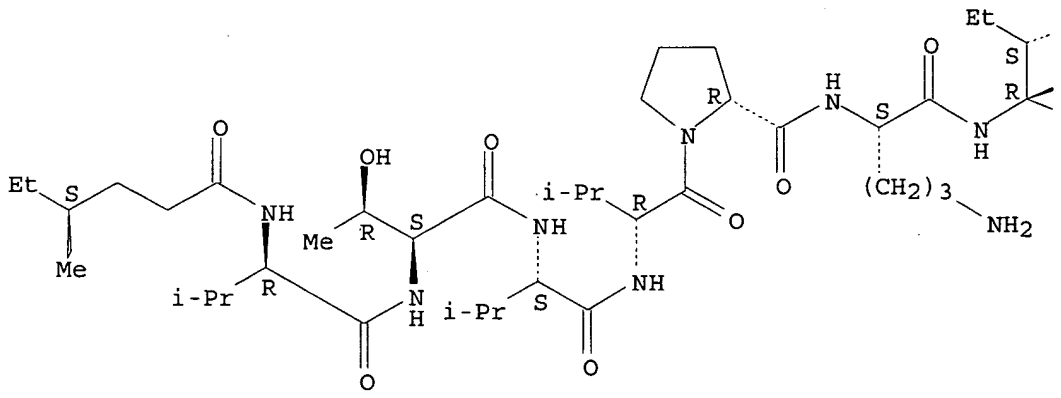
PAGE 1-B



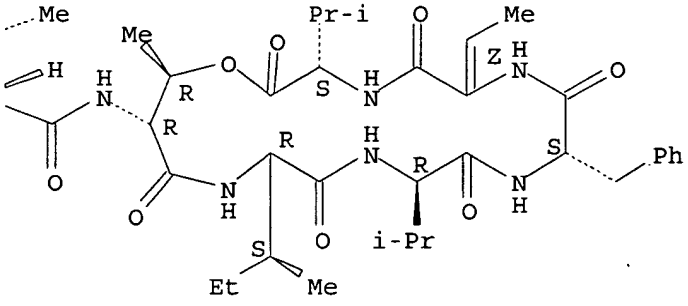
RN 681272-30-0 HCAPLUS
CN Kahalalide F, 1-[N-[(4S)-4-methyl-1-oxohexyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



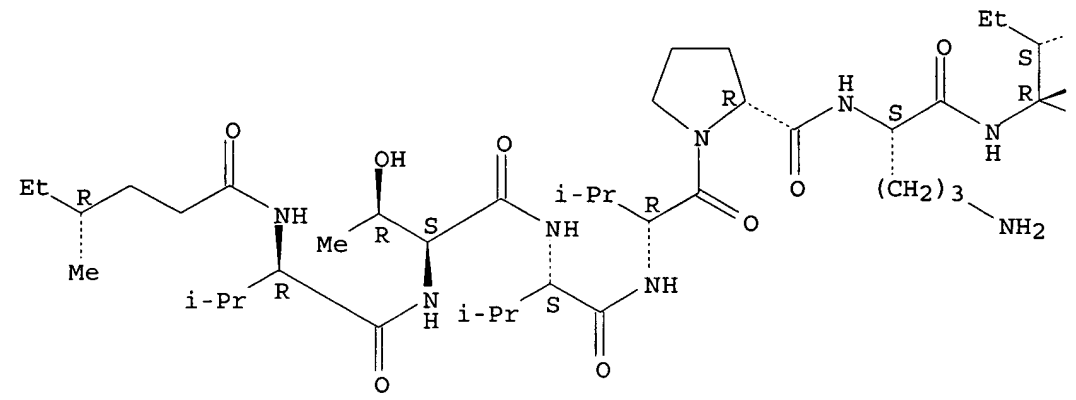
PAGE 1-B



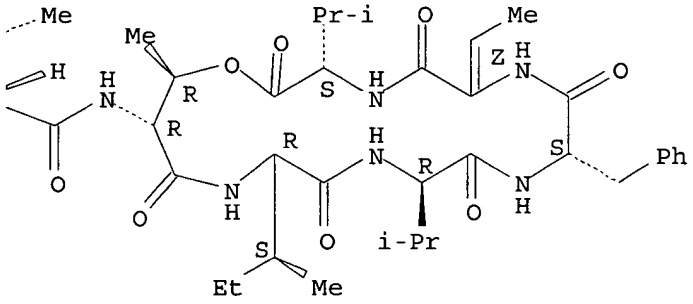
RN 681272-31-1 HCAPLUS
CN Kahalalide F, 1-[N-[(4R)-4-methyl-1-oxohexyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 25 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:28665 HCAPLUS
DOCUMENT NUMBER: 141:140738
TITLE: Conformational analysis of natural marine cyclopeptides with anti-tumor properties
AUTHOR(S): Giralt, Ernest; Gairi, Margarida; Salvatella, Xavier; Rodriguez-Mias, Ricard Aleix; Jimenez, Jose Carlos; Lopez-Macia, Angel; Caba, Josep Maria; Cardenas, Francisco; Feliz, Miguel; Lloyd-Williams, Paul; Albericio, Fernando
CORPORATE SOURCE: Institut de Recerca Biomedica de Barcelona (IRBB-PCB), Universitat de Barcelona, Barcelona, 08028, Spain
SOURCE: Peptides 2002, Proceedings of the European Peptide Symposium, 27th, Sorrento, Italy, Aug. 31-Sept. 6, 2002 (2002), 758-759. Editor(s): Benedetti, Ettore; Pedone, Carlo. Edizioni Ziino: Castellammare di Stabia, Italy.
CODEN: 69EYXG; ISBN: 88-900948-1-8
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report. Conformations of three natural marine cyclopeptides (aplidine, kahalalide F and trunkamide A) with antitumor properties are

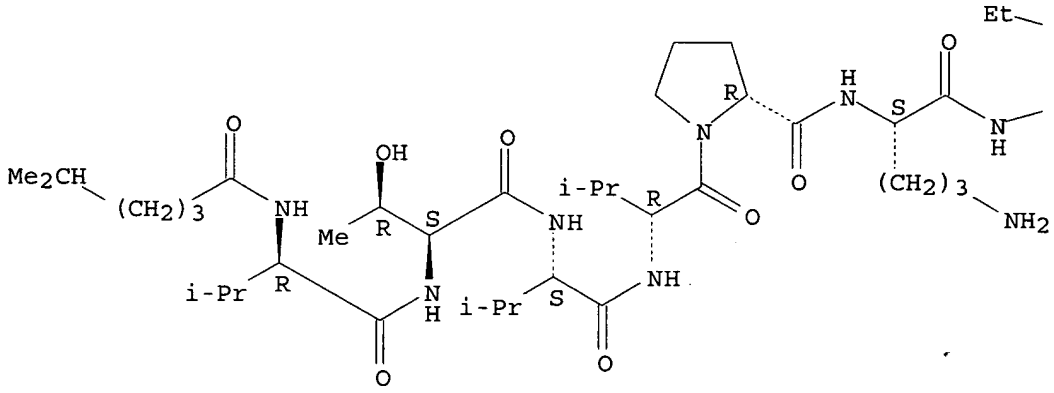
studied using NMR and mol. dynamics calcns. Aplidine exists in CHCl3 as an approx. 1:1 mixture of two slowly interconverting conformations. These conformational changes have no implications in the conformation of the ring that is a very well-defined eight-shaped macrocycle stabilized by a transannular hydrogen bond. Kahalalide F, a depsipeptide, has a flexible tail and a quite rigid macrocycle. Conformation of trunkamide A is observed to be very rigid, dominated by the volume of the dimethylallyl side chains, includes two trans-annular hydrogen bonds, and has two conformationally-restricted residues in the primary structure.

IT 149204-42-2, Kahalalide F
RL: PRP (Properties)
(NMR anal. and mol. dynamics simulations of conformations of marine cyclopeptides with antitumor properties)

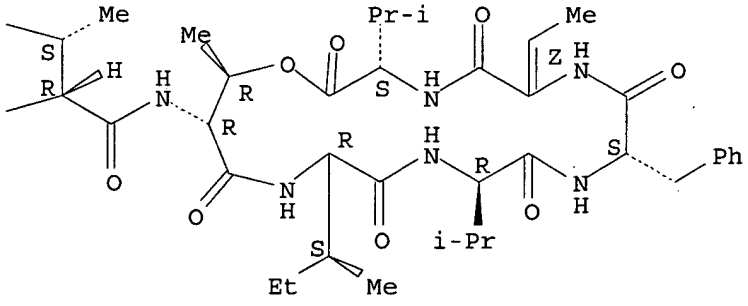
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 26 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:861296 HCAPLUS
DOCUMENT NUMBER: 140:77392
TITLE: Stereochemistry of Kahalalide F

AUTHOR(S): Bonnard, Isabelle; Manzanares, Ignacio; Rinehart, Kenneth L.
CORPORATE SOURCE: Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA
SOURCE: Journal of Natural Products (2003), 66(11), 1466-1470
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:77392

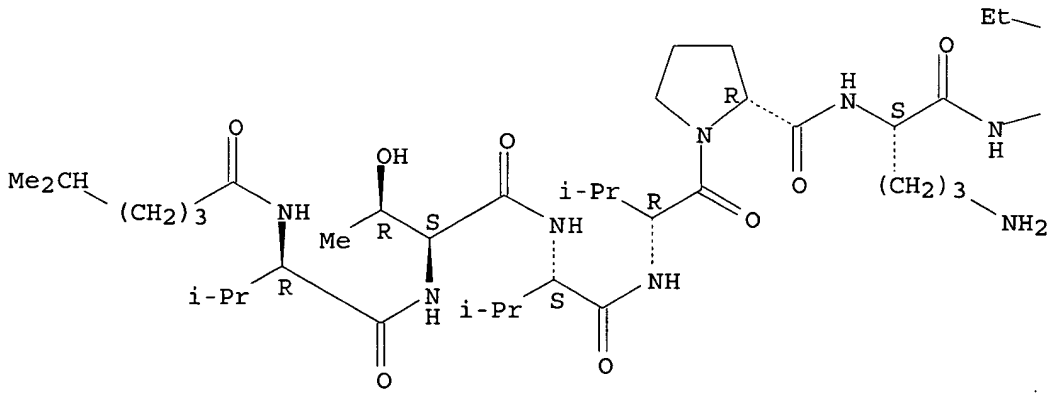
AB The stereochem. of the amino acids in the marine-derived cyclic depsipeptide kahalalide F has been defined by a series of degradation reactions (hydrolysis, ozonolysis, Edman degradation, and Marfey derivatization), yielding smaller fragments of the marine natural product. The results from these reactions agree with the structure originally proposed by Hamann and Scheuer and with the same stereochem. of most of the component amino acids more recently proposed by Goetz, Yoshida, and Scheuer. However, our assignments of D-Val3 and L-Val4 are the reverse of previous assignments made as L-Val3 and D-Val4. The present (reversed) stereochem. is crucial for the antitumor activity of kahalalide F.

IT 149204-42-2, Kahalalide F
RL: BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(stereochem. detns. for valines3,4 of kahalalide F via hydrolysis, ozonolysis, Edman degradation, and Marfey derivatization reactions)

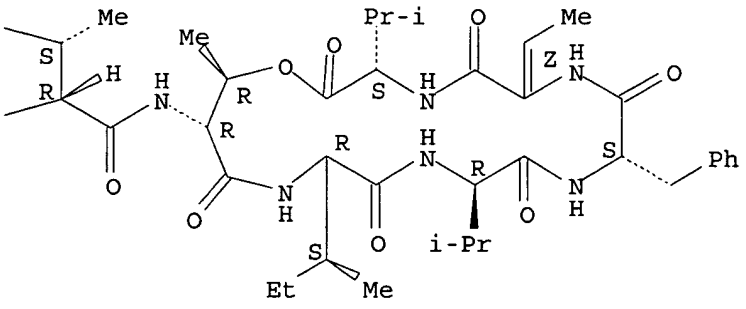
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



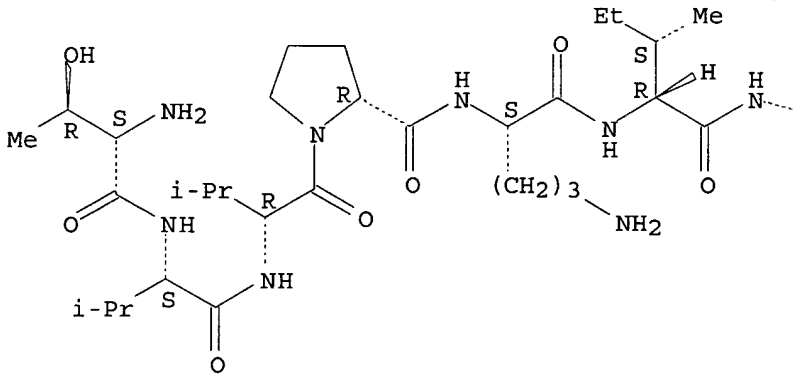
PAGE 1-B



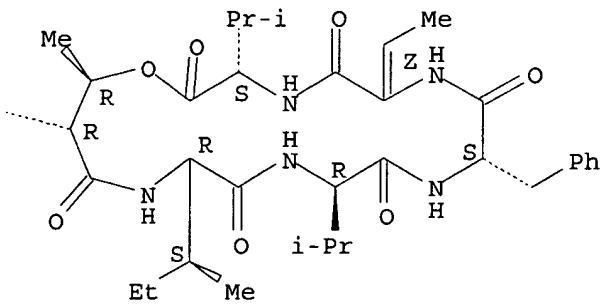
IT 639819-39-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereochem. detns. for valines3,4 of kahalalide F via hydrolysis, ozonolysis, Edman degradation, and Marfey derivatization reactions)
RN 639819-39-9 HCAPLUS
CN L-Valine, L-threonyl-L-valyl-D-valyl-D-prolyl-L-ornithyl-D-alloisoleucyl-D-allothreonyl-D-alloisoleucyl-D-valyl-L-phenylalanyl-(2Z)-2-amino-2-butenoyl-, (12→7)-lactone (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

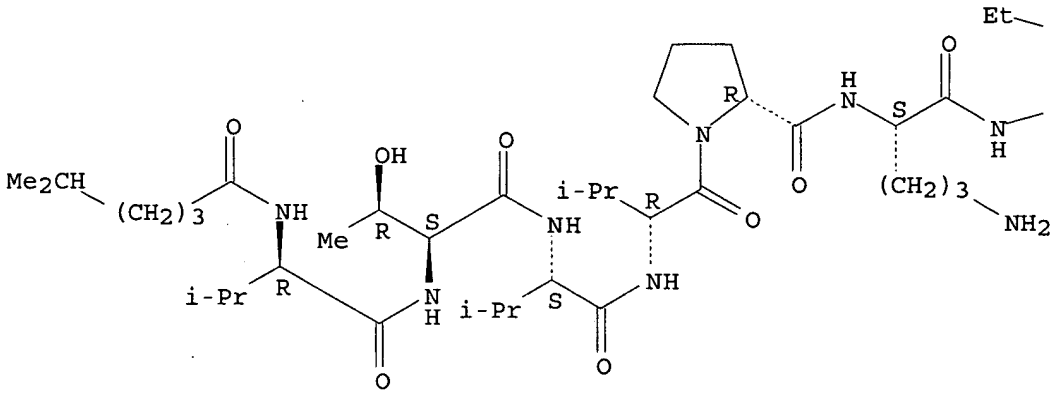
L12 ANSWER 27 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:848751 HCAPLUS
DOCUMENT NUMBER: 140:385585
TITLE: In vitro toxicity of three new antitumoral drugs (trabectedin, aplidin, and kahalalide F) on hematopoietic progenitors and stem cells
AUTHOR(S): Gomez, Susana G.; Bueren, Juan A.; Faircloth, Glynn T.; Jimeno, Jose; Albella, Beatriz
CORPORATE SOURCE: PharmaMar, Madrid, Spain
SOURCE: Experimental Hematology (New York, NY, United States) (2003), 31(11), 1104-1111
CODEN: EXHMA6; ISSN: 0301-472X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: In addition to neutropenias and/or thrombocytopenias as a short-term effect, antineoplastics also can produce long-term effects as a consequence of damage to the hematopoietic stem cells. The aim of the present study was to evaluate the toxicity of three marine-derived antineoplastics on murine hematopoietic stem cells. These antitumoral compds. currently are being evaluated in patients in phase II (aplidin and kahalalide F) and phase II/III (trabectedin) clin. trials. Materials and methods: Long-term competitive repopulating assays were performed in mice to analyze toxic effects on the hematopoietic stem cells responsible for the multipotential long-term repopulation of hematopoiesis. Furthermore, granulocytic and T- and B-lymphoid lineages were studied, as well as myeloid (CFU-GM) and megakaryocytic (CFU-Meg) progenitors. Results: When cells were treated in vitro for 24 h with CFU-GM IC50 dose of trabectedin (9.59 ± 4.96 nM), no significant effects were observed in the stem cells. The dose of trabectedin that produced 90% of inhibition in CFU-GM (IC90: 23.71 ± 1.27 nM) only inhibited 45% survival of stem cells. Doses of aplidin that produced redns. of 50% (56.9 ± 13.32 nM) or 90% (195.88 ± 21.39 nM) in myeloid progenitors did not show any effect on hematopoietic stem cells. Kahalalide F did not show any toxic effect in either short-term or long-term repopulating cells up to 10 μM. Conclusions. Our data show that the hematopoietic stem cells effects of antitumoral drugs can be properly characterized by the murine competitive repopulating assays. Our results suggest that long-term myelosuppression as a consequence of trabectedin, aplidin, or kahalalide F treatment would not be expected.

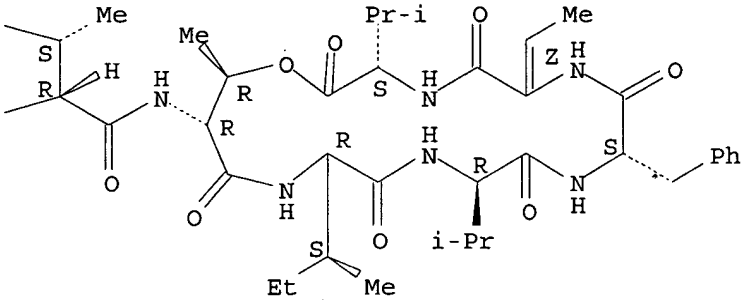
IT 149204-42-2, Kahalalide F
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(study of effect of antitumoral drugs trabectedin, kahalalide F, aplidin on murine hematopoietic stem cells)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 28 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:800266 HCAPLUS
DOCUMENT NUMBER: 140:156903
TITLE: Kahalalide F, a new marine-derived compound, induces oncosis in human prostate and breast cancer cells
AUTHOR(S): Suarez, Yajaira; Gonzalez, Laura; Cuadrado, Ana; Berciano, Maite; Lafarga, Miguel; Munoz, Alberto
CORPORATE SOURCE: Pharma Mar S.A., Instituto de Investigaciones Biomedicas "Alberto Sols", Consejo Superior de Investigaciones Cientificas-Universidad Autonoma de Madrid, Madrid, Spain
SOURCE: Molecular Cancer Therapeutics (2003), 2(9), 863-872
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kahalalide F (KF) is a novel antitumor drug of marine origin under clin. investigation. KF showed a potent cytotoxic activity against a panel of human prostate and breast cancer cell lines, with IC50 ranging from 0.07 μM (PC3) to 0.28 μM (DU145, LNCaP, SKBR-3, BT474, MCF7). Importantly, nontumor human cells (MCF10A, HUVEC, HMEC-1, IMR90) were 5-40 times less sensitive to the drug (IC50 = 1.6-3.1 μM). KF cytotoxicity

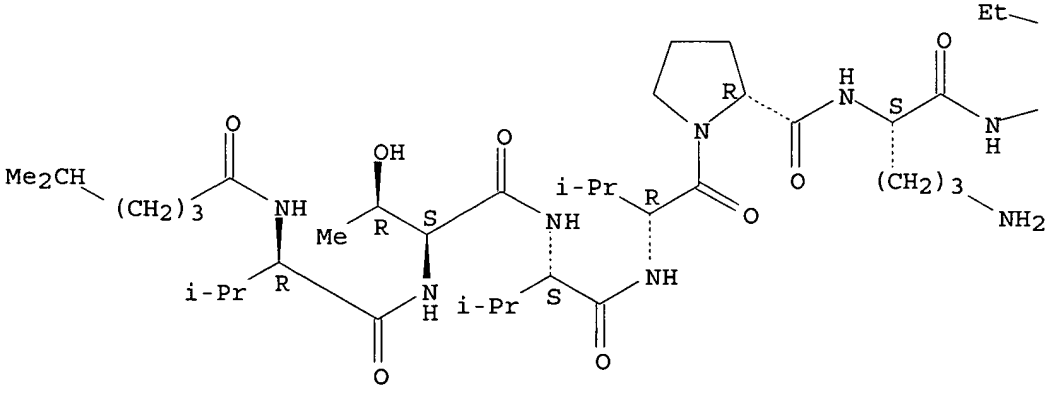
did not correlate with the expression level of the multidrug resistance MDR1 and of the Tyr kinase HER2/NEU, and only slightly by the anti-apoptotic BCL-2 protein. KF action was triggered rapidly by short pulse treatments (15 min caused 50% maximum cytotoxicity). Neither a general caspase inhibitor (Z-VAD-fmk) nor transcription or translation inhibitors (actinomycin D, cycloheximide) blocked KF action. Flow cytometry anal. revealed that KF induced neither cell-cycle arrest nor apoptotic hypodiploid peak. Using mitochondrial (JC-1)- and lysosomal (LysoTracker Green, Acridine Orange)-specific fluorophores, the authors detected loss of mitochondrial membrane potential and of lysosomal integrity following KF treatment. Confocal laser and electron microscopy revealed that KF-treated cells underwent a series of profound alterations including severe cytoplasmic swelling and vacuolization, dilation and vesiculation of the endoplasmic reticulum, mitochondrial damage, and plasma membrane rupture. In contrast, the cell nucleus showed irregular clumping of chromatin into small, condensed masses, while chromatin disappeared from other nuclear domains, but the nuclear envelope was preserved and no DNA degradation was detected. Together, these data indicate that KF induces cell death via oncosis preferentially in tumor cells.

IT 149204-42-2, Kahalalide F
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kahalalide F, a new marine-derived compound, induces oncosis in human prostate and breast cancer cells)

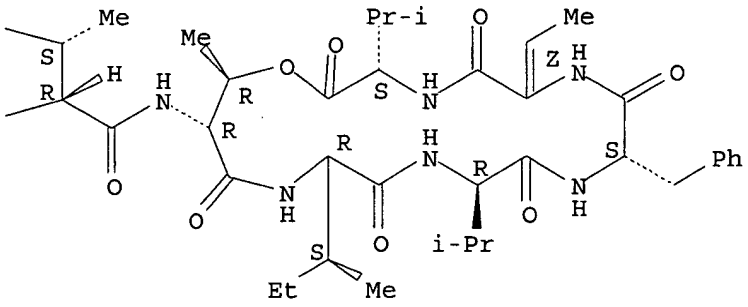
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

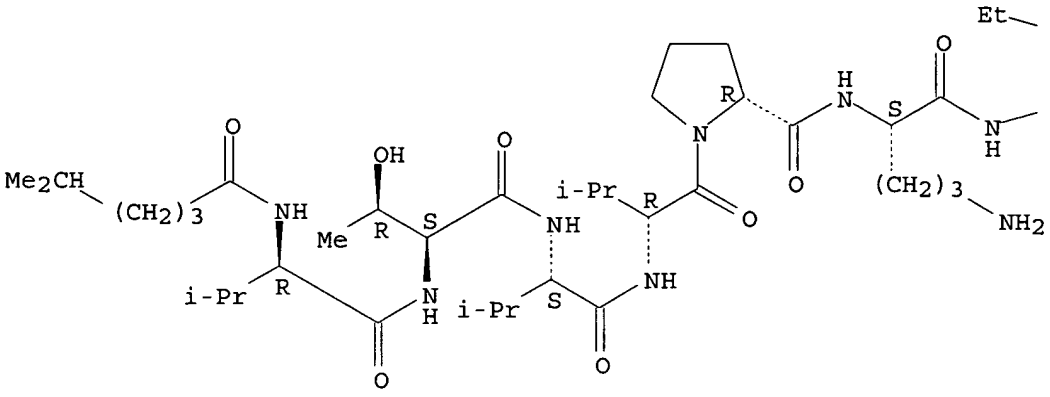


REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

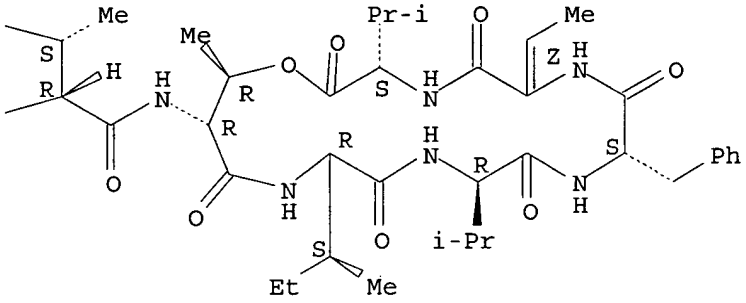
L12 ANSWER 29 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:509479 HCAPLUS
DOCUMENT NUMBER: 140:146458
TITLE: Kahalalide F: synthesis and structural determination
AUTHOR(S): Lopez-Macia, Angel; Jimenez, Jose Carlos; Royo, Miriam; Giralt, Ernest; Albericio, Fernando
CORPORATE SOURCE: Department of Organic Chemistry, University of Barcelona, Barcelona, E-08028, Spain
SOURCE: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 245-246. Editor(s): Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK: Paris, Fr.
CODEN: 69EDWK; ISBN: 2-84254-048-4
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report. Kahalalide F is a cyclic depsipeptide isolated from the Sacoglossan mollusc Elysia rufescens and the green alga Bryopsis sp. Kahalalide F and a diastereomer were prepared by the solid-phase method and their structures determined by 1H NMR.
IT 149204-42-2P, Kahalalide f 354112-37-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and structural determination of kahalalide F and diastereomer)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



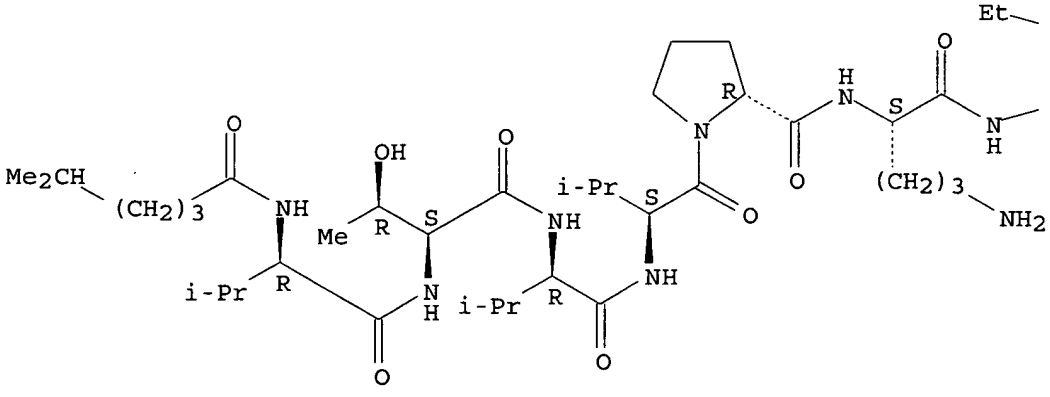
PAGE 1-B



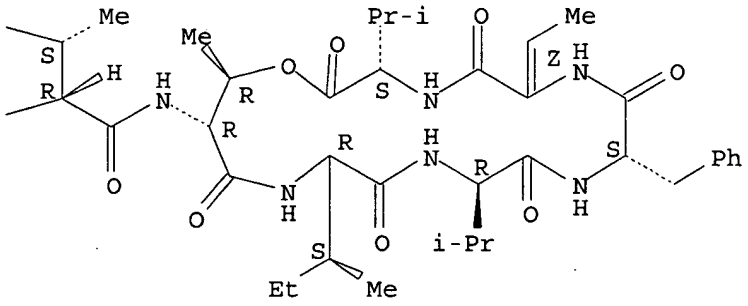
RN 354112-37-1 HCAPLUS
CN Kahalalide F, 3-D-valine-4-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 30 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:456011 HCAPLUS
DOCUMENT NUMBER: 139:390403
TITLE: Development of marine-derived anti-cancer compounds
AUTHOR(S): Taguchi, Tetsuo
CORPORATE SOURCE: Osaka University, Japan
SOURCE: Gan to Kagaku Ryoho (2003), 30(5), 579-588
CODEN: GTKRDX; ISSN: 0385-0684
PUBLISHER: Gan to Kagaku Ryohosha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

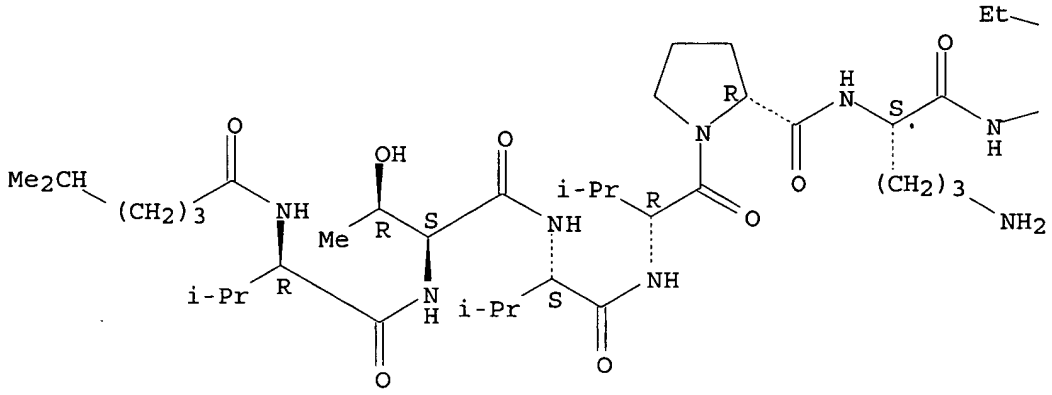
AB A review. The marine environment offers a rich source of natural products with potential therapeutic application. Marine organisms have evolved the enzymic capability to produce potent chemical entitles that make them promising sources of innovative cytotoxic compds. Prominent in the identification and development of novel anti-cancer agents from marine sources is the Spanish biotechnol. company, Pharma Mar, which currently has a large number of oncol. products in late preclin. and clin. development. These include: Ecteinascidin-743 (ET-743), Aplidin, Kahalalide F and ES-285. Many of these innovative compds. have novel mechanisms of antitumor action that have yet to be fully elucidated.

IT 149204-42-2, Kahalalide F
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development of marine-derived anti-cancer compds.)

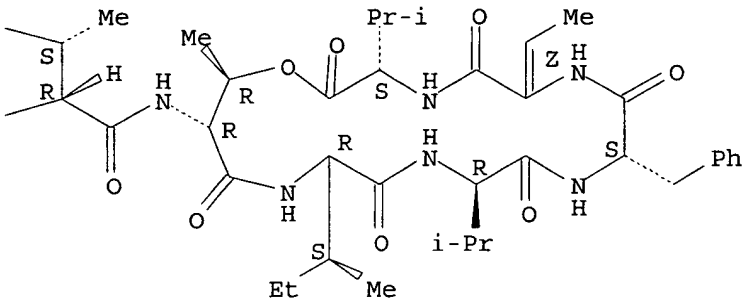
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 31 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:425678 HCAPLUS
DOCUMENT NUMBER: 140:111653
TITLE: Solid-phase synthesis of marine cyclic peptides with antitumoral activity
AUTHOR(S): Lopez-Macia, Angel; Caba, Josep M.; Jimenez, Jose C.; Salvatella, Xavier; Varon, Sonia; Royo, Miriam; Rodriguez, Ignacio; Manzanares, Ignacio; Giralt, Ernest; Albericio, Fernando
CORPORATE SOURCE: Department of Organic Chemistry, University of Barcelona, Barcelona, 08028, Spain
SOURCE: Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids--Small Molecule Organic Chemistry Diversity, Collected Papers, International Symposium, 7th, Southampton, United Kingdom, Sept. 18-22, 2001 (2002), Meeting Date 2001, 13-16. Editor(s): Epton, Roger. Mayflower Worldwide Ltd.: Kingswinford, UK. CODEN: 69DYT7; ISBN: 0-9515735-4-3
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report. Two cyclic peptides, kahalalide F and trunkamide A, were prepared by the solid phase method and are currently in clin. phase I and preclin. trials for treatment of cancer, resp. Kahalalide F is a

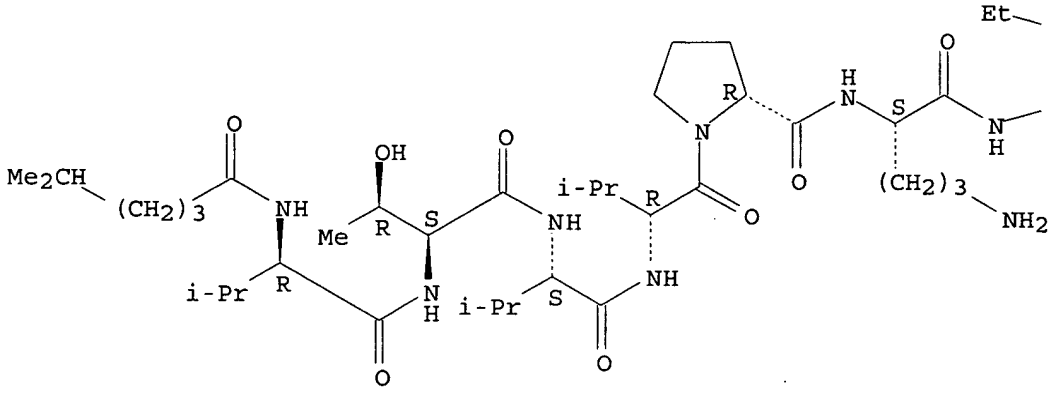
cyclic tridecapeptide containing an ester bond between two β-branched and sterically hindered amino acids, didehydroamino butyric acid, and a hydrophobic sequence with two fragments containing several β-branched amino acids in a row. Trunkamide A is a cyclic heptapeptide which contains hydroxy side-chain amino acids with the hydroxy function modified as dimethylallyl ethers and a thiazoline ring.

IT 149204-42-2P, Kahalalide F
RL: SPN (Synthetic preparation); PREP (Preparation)
(solid-phase synthesis of marine cyclic peptides with antitumoral activity)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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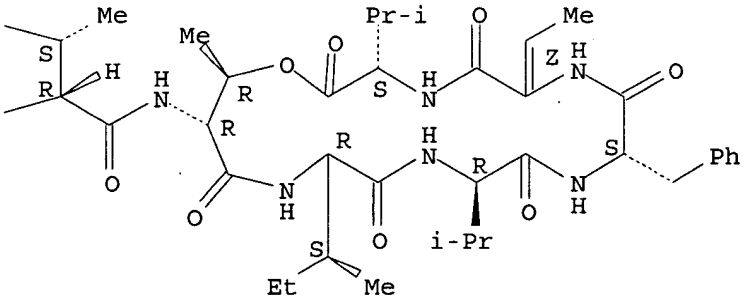

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 32 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:319736 HCAPLUS
DOCUMENT NUMBER: 138:331673
TITLE: Kahalalide compounds for use in cancer therapy
INVENTOR(S): Jimeno, Jose; Lopez, Lazaro Luis; Ruiz Casado, Ana; Izquierdo, Miguel Angel; Paz-Ares, Luis; Trigo, Jose Manuel; Schellens, Jan

PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003033012	A1	20030424	WO 2002-GB4735	20021018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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WO 2002036145	A2	20020510	WO 2001-GB4821	20011031
WO 2002036145	A3	20021017		
WO 2002036145	C1	20031023		
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CA 2462639	AA	20030424	CA 2002-2462639	20021018
EP 1435990	A1	20040714	EP 2002-801430	20021018
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CA 2501089	AA	20040429	CA 2003-2501089	20031020
WO 2004035613	A2	20040429	WO 2003-US33207	20031020
WO 2004035613	A3	20040729		
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AU 2003285911	A1	20040504	AU 2003-285911	20031020
BR 2003015489	A	20050823	BR 2003-15489	20031020
EP 1572726	A2	20050914	EP 2003-779140	20031020
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1705677	A	20051207	CN 2003-80101647	20031020
JP 2006517195	T2	20060720	JP 2005-501483	20031020
US 2005054555	A1	20050310	US 2004-492670	20041103
ZA 2005002926	A	20060222	ZA 2005-2926	20050411

NO 2005002379	A	20050715	NO 2005-2379		20050513
PRIORITY APPLN. INFO.:			US 2001-348449P	P	20011019
			WO 2001-GB4821	A	20011031
			GB 2002-22409	A	20020926
			US 2000-244471P	P	20001031
			US 2000-246229P	P	20001106
			WO 2002-GB4735	W	20021018
			GB 2003-4367	A	20030226
			GB 2003-14725	A	20030624
			WO 2003-US33207	W	20031020

OTHER SOURCE(S): MARPAT 138:331673

AB Procedures for clin. trials of kahalalide compds. are provided, leading to new formulations of kahalalide compds.

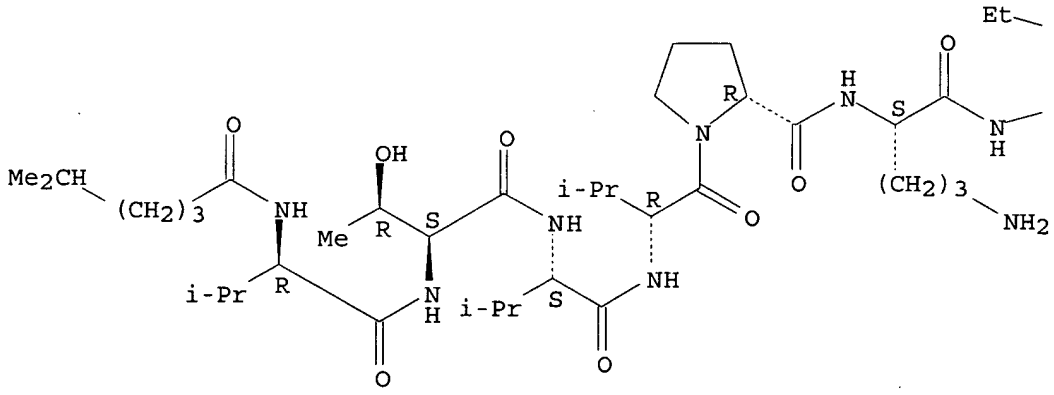
IT 149204-42-2, Kahalalide F
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kahalalide compds. for cancer therapy)

RN 149204-42-2 HCAPLUS

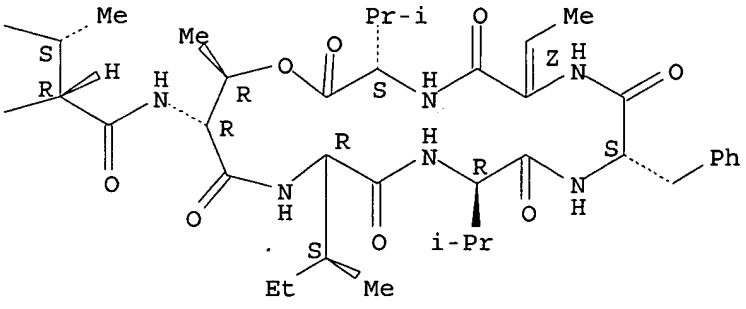
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 33 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:170633 HCAPLUS
DOCUMENT NUMBER: 138:250145
TITLE: Marine natural products as prototype agrochemical agents
AUTHOR(S): Peng, Jiangnan; Shen, Xiaoyu; El Sayed, Khalid A.; Dunbar, D. Charles; Perry, Tony L.; Wilkins, Scott P.; Hamann, Mark T.; Bobzin, Steve; Huesing, Joseph; Camp, Robin; Prinsen, Mike; Krupa, Dan; Wideman, Margaret A.
CORPORATE SOURCE: Department of Pharmacognosy and National Center for the Development of Natural Products, School of Pharmacy, The University of Mississippi, University, MS, 38677, USA
SOURCE: Journal of Agricultural and Food Chemistry (2003), 51(8), 2246-2252
CODEN: JAFCAU; ISSN: 0021-8561
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

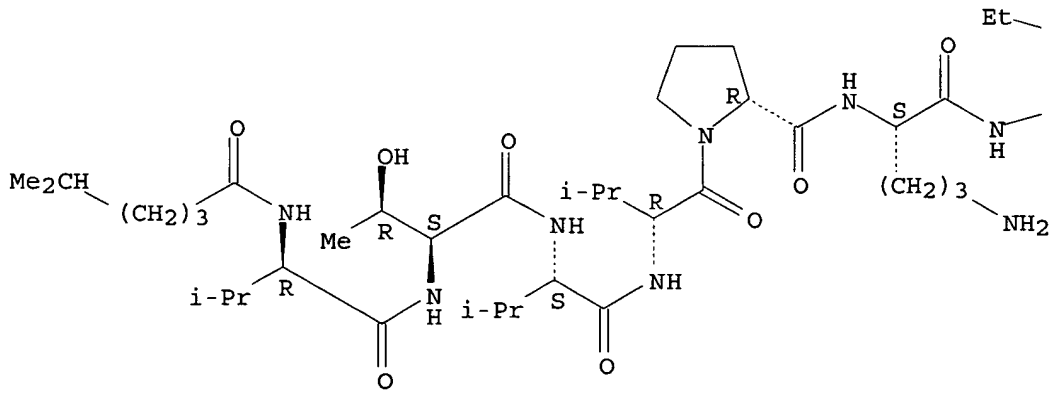
AB In the interest of identifying new leads that could serve as prototype agrochem. agents, 18 structurally diverse marine-derived compds. were examined for insecticidal, herbicidal, and fungicidal activities. Several new classes of compds. have been shown to be insecticidal, herbicidal, and fungicidal, which suggests that marine natural products represent an intriguing source for the discovery of new agrochem. agents.

IT 149204-42-2, Kahalalide F
RL: AGR (Agricultural use); BSU (Biological study, unclassified); BIOL (Biological study); USES (Uses)
(insecticidal, herbicidal, and fungicidal activity of)

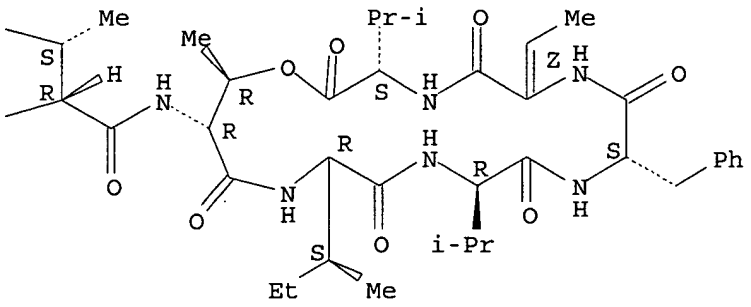
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 34 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:779665 HCAPLUS
DOCUMENT NUMBER: 138:313796
TITLE: Quantitative analysis of the novel depsipeptide anticancer drug Kahalalide F in human plasma by high-performance liquid chromatography under basic conditions coupled to electrospray ionization tandem mass spectrometry
AUTHOR(S): Stokvis, E.; Rosing, H.; Lopez-Lazaro, L.; Rodriguez, I.; Jimeno, J. M.; Supko, J. G.; Schellens, J. H. M.; Beijnen, J. H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Journal of Mass Spectrometry (2002), 37(9), 992-1000
CODEN: JMSPFJ; ISSN: 1076-5174
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kahalalide F (KF) is a novel cyclic depsipeptide anticancer drug which has shown anticancer activity both in vitro and in vivo, especially against human prostate cancer cell lines. To characterize the pharmacokinetics of KF during a phase I clin. trial in patients with androgen-refractory prostate cancer, a method was developed and validated for the quant. anal. of KF in human plasma by HPLC coupled to pos. electrospray ionization tandem mass spectrometry (ESI-MS/MS). Microbore reversed-phase liquid chromatog. (LC) performed with mobile phases containing trifluoroacetic acid, an additive commonly used for separating peptides, resulted in substantial suppression of the signal for KF in ESI-MS/MS. An alternative approach employing a basic mobile phase provided an excellent response to KF when used in the pos. ion mode. Plasma samples were prepared for LC MS/MS by solid-phase extraction on C18 cartridges. The LC separation was performed on a Zorbax Extend C18 column (150 + 2.1 mm., particle size 5 μm) with MeCN-10 mM aqueous NH3 (85:15) as the mobile phase, at a flow-rate of 0.20 mL/min. A butyric acid analog of KF was used as the internal standard The lower limit of quantitation when using a 500-μL sample volume was 1 ng/mL and the linear dynamic range extended to 1000 ng/mL. The interassay accuracy of the assay was -15.1% at the lower limit of quantitation and between -2.68 and -9.05% for quality control solns. ranging in concentration from 2.24 to 715 ng/mL. The interassay precision was 9.91% or better at these concns. The analyte was stable in plasma under all conditions evaluated and for a

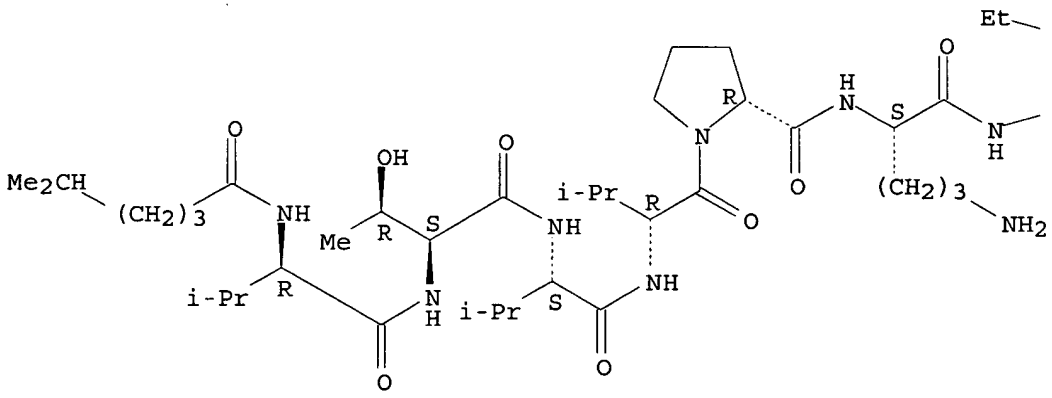
period of 16 h after reconstituting plasma exts. for LC anal. at ambient temperature

IT 149204-42-2, Kahalalide F
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)
(determination of Kahalalide F in human plasma by HPLC/tandem mass spectrometry)

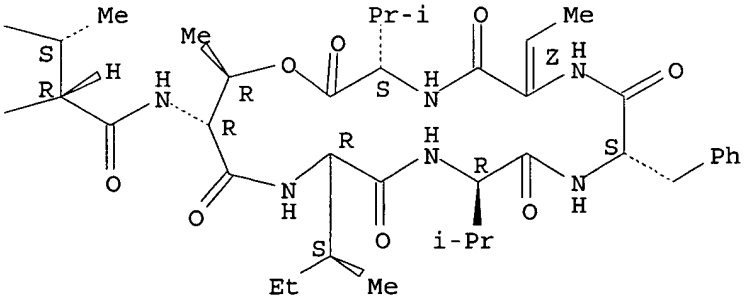
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 35 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:742571 HCAPLUS
DOCUMENT NUMBER: 139:62716
TITLE: Preclinical toxicity studies of kahalalide F, a new anticancer agent: single and multiple dosing regimens in the rat
AUTHOR(S): Brown, Alan P.; Morrissey, Robert L.; Faircloth, Glynn T.; Levine, Barry S.
CORPORATE SOURCE: Toxicology Research Laboratory, University of Illinois at Chicago, Chicago, IL, 60612, USA

SOURCE: Cancer Chemotherapy and Pharmacology (2002), 50(4), 333-340
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

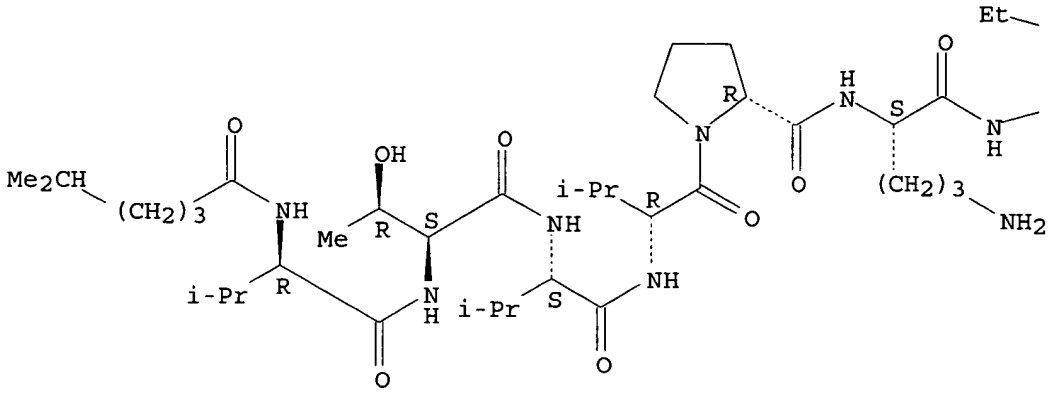
AB Kahalalide F (KF) is a new anticancer agent currently in clin. trials for solid tumors, including prostate cancer. During the preclin. development of this drug, the studies reported here were conducted to determine the acute and multiple dose toxicities of KF when administered i.v. to rats. This dosing route is the intended route of clin. administration. KF was administered i.v. to male and female CD rats using single- and multiple-dose (daily for 5 days) schedules. Animals were observed for clin. signs, and body weight, hematol., and clin. chemical parameters determined Animals were necropsied, gross observations and organ wts. recorded, and numerous tissues were collected and examined microscopically. KF produced lethality at 375 and 450 μg/kg in males and females, resp., and the maximum tolerated dose (MTD) was estimated to be 300 μg/kg (1800 μg/m2). The nervous system appeared to be a potential site of action for the production of lethality. Single-dose administration of KF at 150 and 300 μg/kg produced organ toxicity in which the kidney was the primary target. Injury to distal convoluted tubules was the most toxicol. significant lesion, and was observed on day 4. However, by day 29, resolution of renal toxicity had occurred in the 150-μg/kg group, but only partial resolution was seen at 300 μg/kg. Renal injury correlated with increased serum creatinine, BUN, and kidney wts. at 300 μg/kg, indicating impairment of renal function. Subacute, necrotizing inflammation of bone marrow and peritrabecular osteocyte hyperplasia of bone were seen at 300 μg/kg on day 4, with recovery thereafter. Injury to blood vessels and surrounding tissue at the injection site were produced by KF, likely due to local cytotoxicity. In general, reversibility of toxicity was seen at 150 μg/kg but not at 300 μg/kg. When KF was administered once daily for five consecutive days at a dose of 80 μg/kg per day (400 μg/kg total dose), slightly decreased body weight gain was the primary drug-related effect. Therefore, the no-adverse-effect dose was at or near 80 μg/kg per day (480 μg/m2 per day). These findings demonstrate that fractionation of a lethal or MTD dose of KF by daily administration for 5 days reduces drug-induced toxicity, and appears to be a viable option for the clin. evaluation of KF for the treatment of cancer.

IT 149204-42-2, Kahalalide F
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preclin. toxicity studies of anticancer agent kahalalide F)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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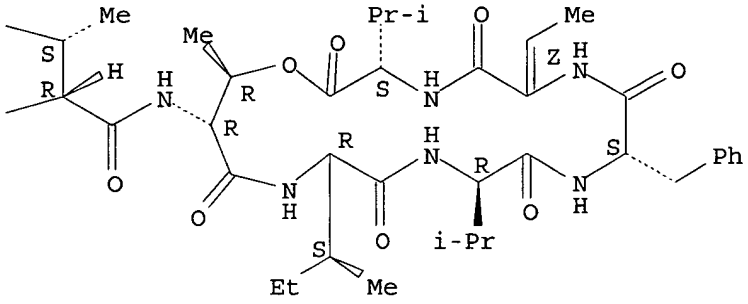


REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 36 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:692319 HCAPLUS
DOCUMENT NUMBER: 138:271948
TITLE: Solid-phase total syntheses of trunkamide A and kahalalide F, cyclic peptides of marine origin
AUTHOR(S): Albericio, Fernando; Caba, Josep M.; Lopez-Macia, Angel; Jimenez, Jose C.; Carrascal, Marta; Sole, Laia; Rodriguez, Ignacio; Manzanares, Ignacio; Royo, Miriam; Giralt, Ernest
CORPORATE SOURCE: Department of Organic Chemistry, University of Barcelona, Barcelona, E-08028, Spain
SOURCE: Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium, San Diego, CA, United States, June 9-14, 2001 (2001), 217-219. Editor(s): Lebl, Michal; Houghten, Richard A. American Peptide Society: San Diego, Calif.
CODEN: 69DBAL; ISBN: 0-9715560-0-8
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report. Two cyclic peptides of marine origin, Trunkamide A and Kahalalide F, were synthesized. Common features of both syntheses

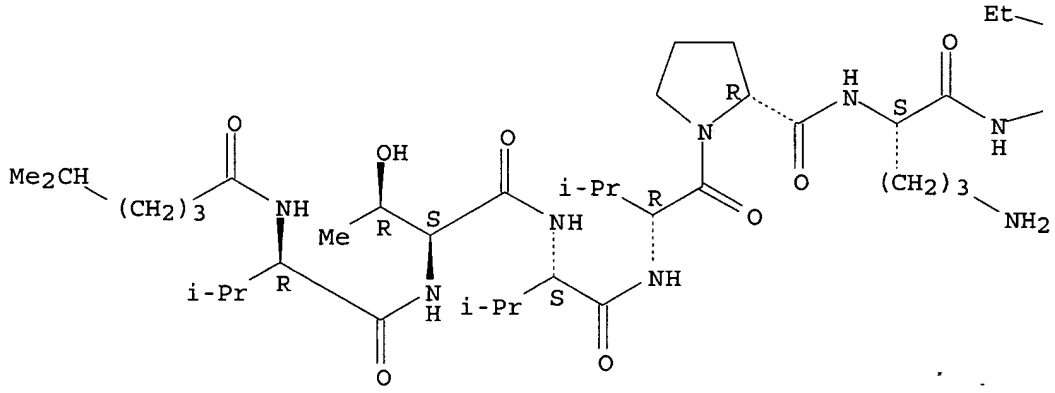
include solid-phase peptide chain elongation using a quasi orthogonal protecting scheme with allyl, t-Bu, and fluorenyl based groups on a chlorotrityl resin.

IT 149204-42-2P, Kahalalide F
RL: SPN (Synthetic preparation); PREP (Preparation)
(solid-phase total syntheses of trunkamide A and kahalalide F, cyclic peptides of marine origin)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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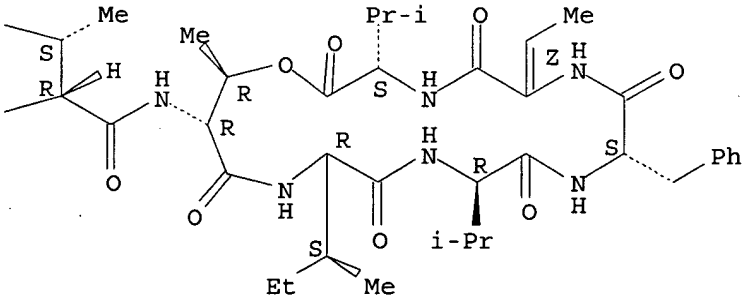


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 37 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:521462 HCAPLUS
DOCUMENT NUMBER: 137:88442
TITLE: Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms
INVENTOR(S): Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S): Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE1	20020102
WO 2002053138	A3	20020919		
W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG				
AU 2002219472	A1	20020716	AU 2002-219472	20020102
EP 1351678	A2	20031015	EP 2002-727007	20020102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004092583	A1	20040513	US 2004-250535	20040102
PRIORITY APPLN. INFO.:			IE 2001-2 A	20010102
			WO 2002-IE1 W	20020102

OTHER SOURCE(S): MARPAT 137:88442

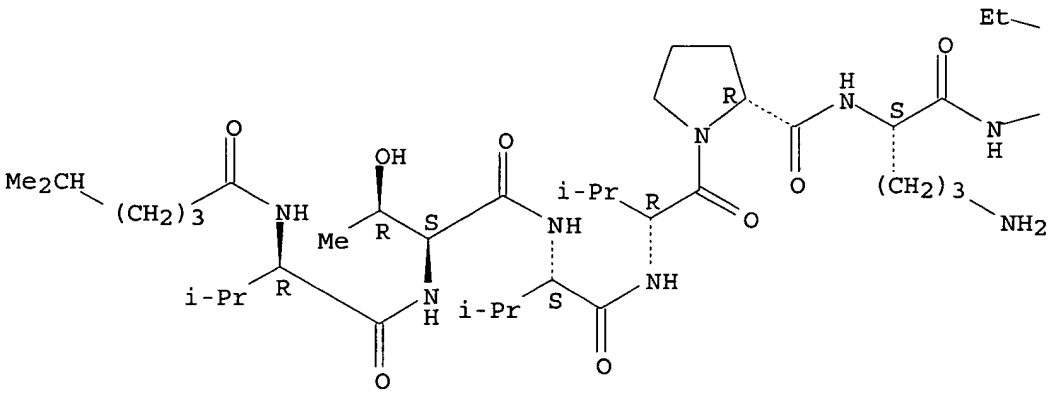
AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immunodysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixture showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

IT 149204-42-2, Kahalalide F
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation further including; incensole and furanogermacrens and compds. as antitumor and antimicrobial agents)

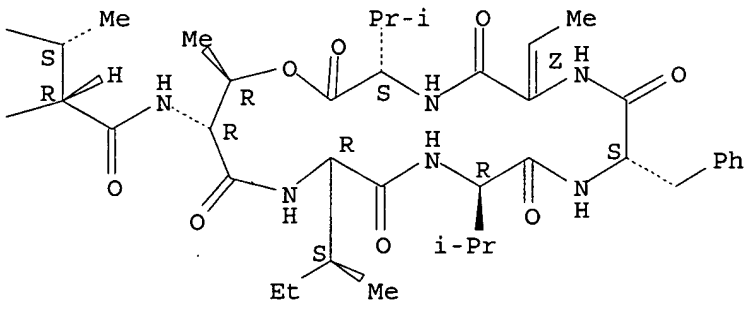
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 38 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:353299 HCAPLUS
DOCUMENT NUMBER: 136:359641
TITLE: Kahalalide F formulations for antitumor use
INVENTOR(S): Ruffles, Graham Keith; Faircloth, Glynn Thomas; Nuyen, Bastian; Weitman, Steve
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036145	A2	20020510	WO 2001-GB4821	20011031
WO 2002036145	A3	20021017		
WO 2002036145	C1	20031023		
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CA 2425627	AA	20020510	CA 2001-2425627	20011031
AU 2002010749	A5	20020515	AU 2002-10749	20011031
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EP 1330258	B1	20051228		
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JP 2004512370	T2	20040422	JP 2002-538956	20011031
CN 1568192	A	20050119	CN 2001-818271	20011031
NZ 525243	A	20050128	NZ 2001-525243	20011031
AT 314084	E	20060115	AT 2001-978654	20011031
ES 2256305	T3	20060716	ES 2001-1978654	20011031
CA 2462639	AA	20030424	CA 2002-2462639	20021018
WO 2003033012	A1	20030424	WO 2002-GB4735	20021018
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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1435990	A1	20040714	EP 2002-801430		20021018
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ZA 2003003136	A	20040723	ZA 2003-3136		20030423
NO 2003001860	A	20030630	NO 2003-1860		20030425
US 2004067895	A1	20040408	US 2003-399571		20031114
PRIORITY APPLN. INFO.:			US 2000-244471P	P	20001031
			US 2000-246229P	P	20001106
			US 2001-348449P	P	20011019
			WO 2001-GB4821	W	20011031
			GB 2002-22409	A	20020926
			WO 2002-GB4735	W	20021018

AB New formulations and new uses of kahalalide F are provided for antitumor application against neuroblastomas or dedifferentiated or mesenchymal chondrosarcomas or osteosarcomas.

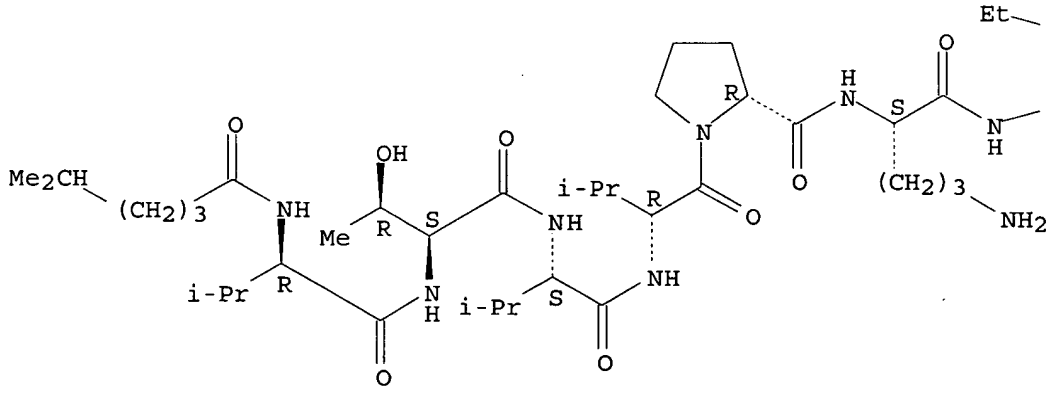
IT 149204-42-2, Kahalalide F
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(kahalalide F formulations for antitumor use)

RN 149204-42-2 HCAPLUS

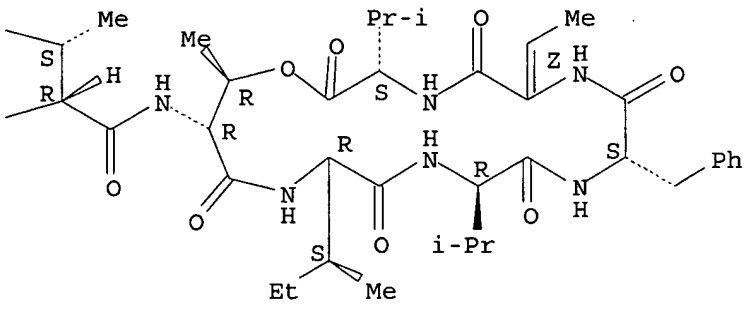
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



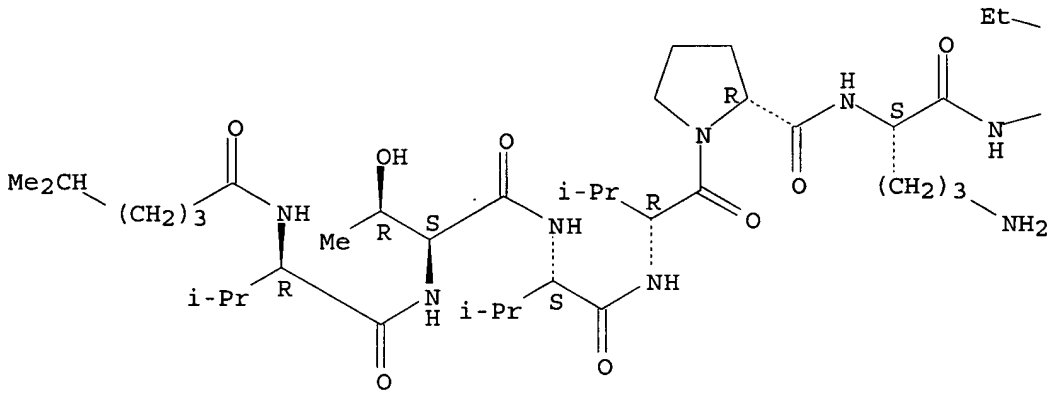
L12 ANSWER 39 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:924856 HCAPLUS
DOCUMENT NUMBER: 136:315111
TITLE: Development of an HPLC method with UV detection for the pharmaceutical quality control of the novel marine anticancer agent kahalalide F
AUTHOR(S): Nuijen, B.; Bouma, M.; Floriano, P.; Manada, C.; Rosing, H.; Stokvis, E.; Kettenes-van den Bosch, J. J.; Bult, A.; Beijnen, J. H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital, The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Journal of Liquid Chromatography & Related Technologies (2001), 24(20), 3141-3155
CODEN: JLCTFC; ISSN: 1082-6076
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kahalalide F is a cyclic depsipeptide derived from the marine mollusc Elysia rufescens, an organism living in the seas near Hawaii. On the basis of its in vitro and in vivo selectivity, kahalalide F is currently developed as a potential anticancer agent against androgen independent prostate tumors. The development and validation of a reversed-phase high performance liquid chromatog. (RP-HPLC) method with ultra-violet (UV) detection for the quantification and purity determination of kahalalide F in raw drug substance and pharmaceutical dosage form was described. Linear calibration curves in the range of 0.5-12.5 μg/mL of kahalalide F with correlation coeffs. > 0.999 were obtained. Within-run and between-run precisions were ≤ 3.0% and accuracy was within 100.4-103.2%. The assay proved selective, as determined by stress-testing, confirming its stability indicating capacity. Using liquid chromatog.-mass spectrometry (LC-MS) anal., kahalalide G, the hydrolyzed open-chain analog of kahalalide F, appeared upon heating and in acidic media. Furthermore, it was shown that kahalalide F remains its integrity in the freeze-dried pharmaceutical dosage form.

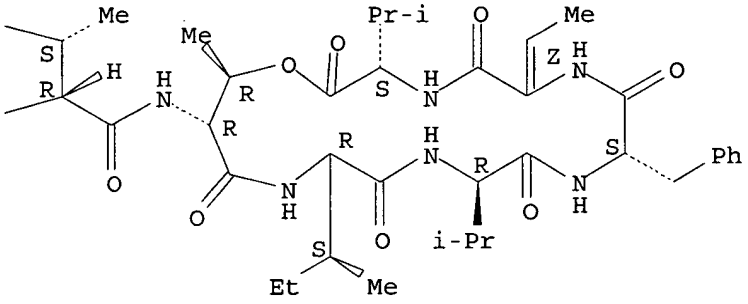
IT 149204-42-2, Kahalalide F
RL: ANT (Analyte); ANST (Analytical study)
(determination of anticancer agent Kahalalide F by HPLC with UV detection and comparison to LC-MS method results)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 40 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:849600 HCAPLUS
DOCUMENT NUMBER: 136:99533
TITLE: Chemical defenses of the sacoglossan mollusk Elysia rufescens and its host alga Bryopsis sp.
AUTHOR(S): Becerro, Mikel A.; Goetz, Gilles; Paul, Valerie J.; Scheuer, Paul J.
CORPORATE SOURCE: Department of Chemistry, University of Hawaii at Manoa, Honolulu, HI, 96822, USA
SOURCE: Journal of Chemical Ecology (2001), 27(11), 2287-2291
CODEN: JCECD8; ISSN: 0098-0331
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sacoglossans are a group of opisthobranch mollusks that have been the source of numerous secondary metabolites; however, there are few examples where a defensive ecol. role for these compds. has been demonstrated exptl. We investigated the deterrent properties of the sacoglossan Elysia rufescens and its food alga Bryopsis sp. against natural fish predators. Bryopsis sp. produces kahalalide F, a major depsipeptide that is

accumulated by the sacoglossan and that shows in vitro cytotoxicity against several cancer cell lines. Our data show that both Bryopsis sp. and Elysia rufescens are chemical protected against fish predators, as indicated by the deterrent properties of their exts. at naturally occurring concns. Following bioassay-guided fractionation, we observed that the antipredatory compds. of Bryopsis sp. were present in the butanol and chloroform fractions, both containing the depsipeptide kahalalide F. Antipredatory compds. of Elysia rufescens were exclusively present in the dichloromethane fraction. Further bioassay-guided fractionation led to the isolation of kahalalide F as the only compound responsible for the deterrent properties of the sacoglossan. Our data show that kahalalide F protects both Bryopsis sp. and Elysia rufescens from fish predation. This is the first report of a diet-derived depsipeptide used as a chemical defense in a sacoglossan.

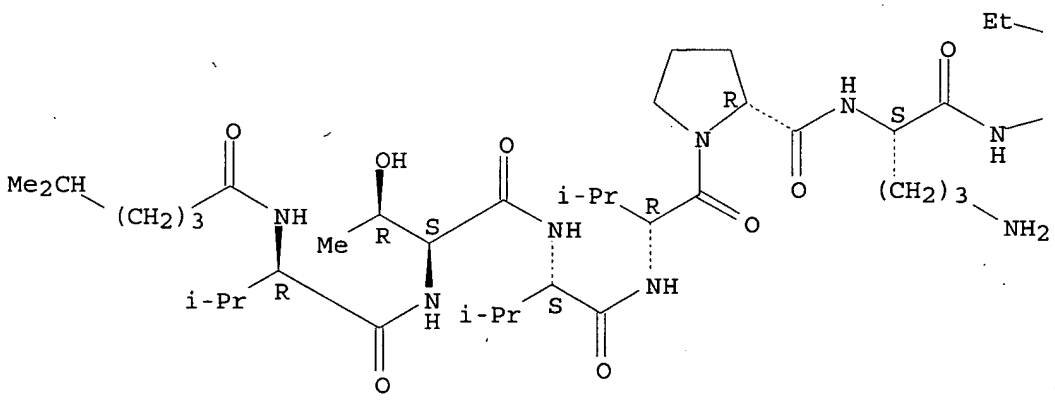
IT 149204-42-2, Kahalalide F
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chemical defenses of sacoglossan mollusk and its host alga against predator fish)

RN 149204-42-2 HCAPLUS

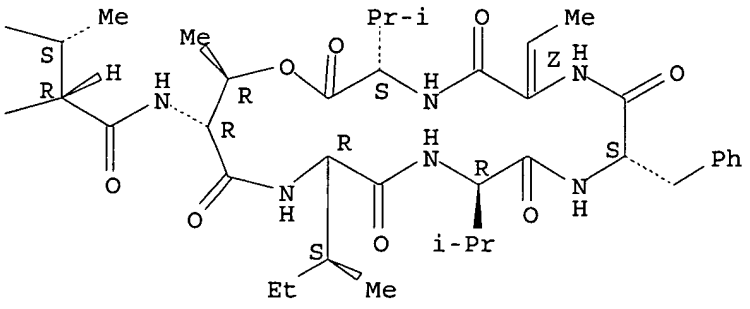
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

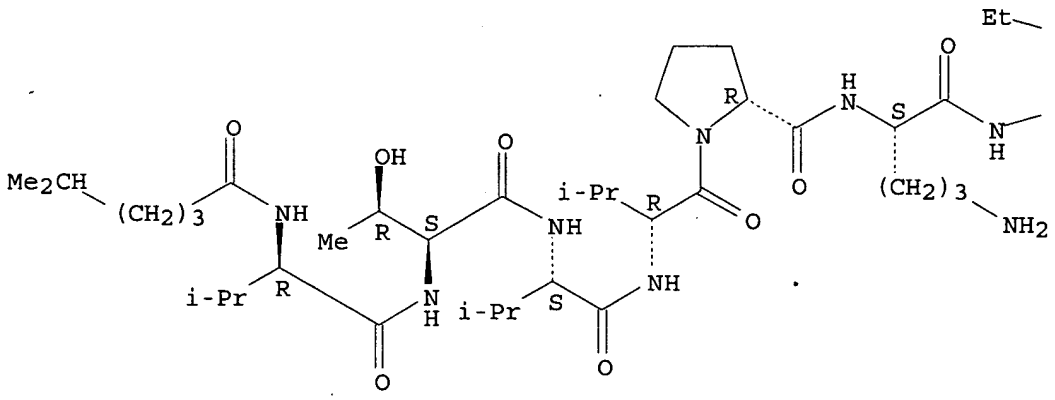
L12 ANSWER 41 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:846704 HCAPLUS
DOCUMENT NUMBER: 137:98856
TITLE: Development of a lyophilized parenteral pharmaceutical formulation of the investigational polypeptide marine anticancer agent kahalalide F
AUTHOR(S): Nuijen, B.; Bouma, M.; Talsma, H.; Manada, C.; Jimeno, J. M.; Lopez-Lazaro, L.; Bult, A.; Beijnen, J. H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Drug Development and Industrial Pharmacy (2001), 27(8), 767-780
CODEN: DDIPD8; ISSN: 0363-9045
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kahalalide F is a novel antitumor agent isolated from the marine mollusk Elysia rufescens; it has shown highly selective in vitro activity against androgen-independent prostate tumors. The purpose of this study was to develop a stable parenteral formulation of kahalalide F to be used in early clin. trials. Solubility and stability of kahalalide F were studied as a function of polysorbate 80 (0.1%-0.5% w/v) and citric acid monohydrate (5-15 mM) concns. using an exptl. design approach. Stabilities of kahalalide F lyophilized products containing crystalline (mannitol) or amorphous (sucrose) bulking agents were studied at +5° and +30°±60% relative humidity (RH) in the dark. Lyophilized products were characterized by IR (IR) spectroscopy and differential scanning calorimetry (DSC). Recovery studies after reconstitution of kahalalide F lyophilized product and further dilution in infusion fluid were carried out to select an optimal reconstitution vehicle. It was found that a combination of polysorbate 80 and citric acid monohydrate is necessary to solubilize kahalalide F. Lyophilized products were considerably less stable with increasing polysorbate 80 and citric acid monohydrate concns., with polysorbate 80 being the major effector. A combination of 0.1% w/v polysorbate 80 and 5 mM citric acid monohydrate was selected for further investigation. Lyophilized products containing sucrose as a bulking agent were more stable compared to the products containing mannitol. The glass transition temperature of the sucrose-based product was determined to be +46°. The amorphous state of the product was confirmed by IR anal. A solution composed of Cremophor EL, ethanol, and water for injection (5%/5%/90% volume/volume/v CEW) kept kahalalide F in solution after reconstitution and further dilution with 0.9% w/v sodium chloride (normal saline) to 1.5 μg/m. A stable lyophilized formulation was presented containing 100 μg of kahalalide F, 100 mg sucrose, 2.1 mg citric acid monohydrate, and 2 mg polysorbate 80 to be reconstituted with a vehicle composed of 5%/5%/90% volume/volume/v CEW and to be diluted further using normal saline.

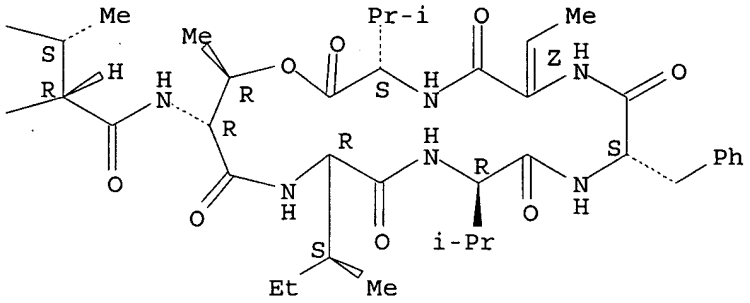
IT 149204-42-2, Kahalalide F
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lyophilized parenteral pharmaceutical formulation of polypeptide marine anticancer agent kahalalide F)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 42 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:781497 HCAPLUS
DOCUMENT NUMBER: 136:86050
TITLE: Synthesis and Structure Determination of Kahalalide F
AUTHOR(S): Lopez-Macia, Angel; Jimenez, Jose Carlos; Royo, Miriam; Giralt, Ernest; Albericio, Fernando
CORPORATE SOURCE: Department of Organic Chemistry, University of Barcelona, Barcelona, 08028, Spain
SOURCE: Journal of the American Chemical Society (2001), 123(46), 11398-11401
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:86050

AB Kahalalide F, the only member of the kahalalide peptide family with important bioactivity, is in clin. trials for treatment of prostate cancer. An efficient solid-phase synthetic approach is reported. Kahalalide F presents several synthetic difficulties: (i) an ester bond between two β-branched and sterically hindered amino acids; (ii) a didehydroamino acid; and (iii) a rather hydrophobic sequence with two fragments containing several β-branched amino acids in a row, one of them terminated with a saturated aliphatic acid. The cornerstones of our strategy

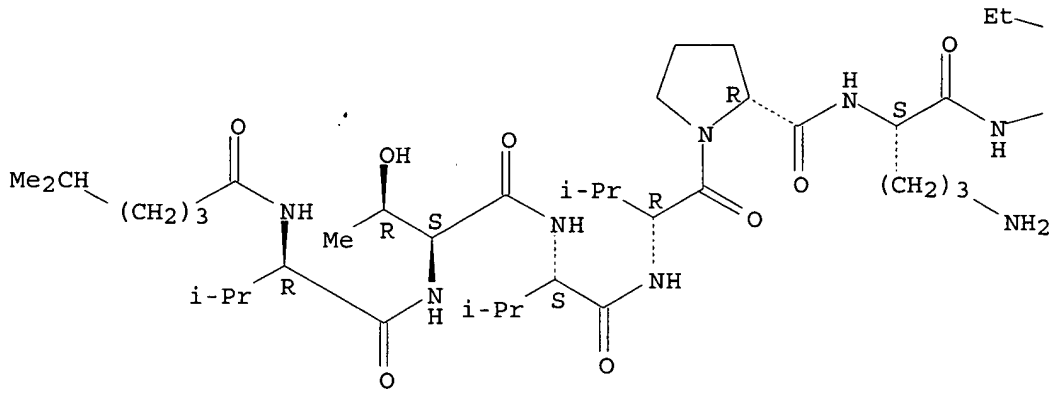
were (i) a quasiorthogonal protecting system with allyl, tert-Bu, fluorenyl, and trityl-based groups, (ii) azabenzotriazole coupling reagents, (iii) formation of the didehydroamino acid residue on the solid phase, and (iv) cyclization and final purification in solution HPLC, high-field NMR, and biol. activity studies showed that the correct stereochem. of the natural product is that proposed by Rinehart et al., whereas the stereochem. proposed by Scheuer et al. is that of a biol. less active diastereoisomer.

IT 149204-42-2P, Kahalalide F 354112-37-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(solid-phase synthesis, structure detns. and biol. activity of kahalalide F and its diastereomer)

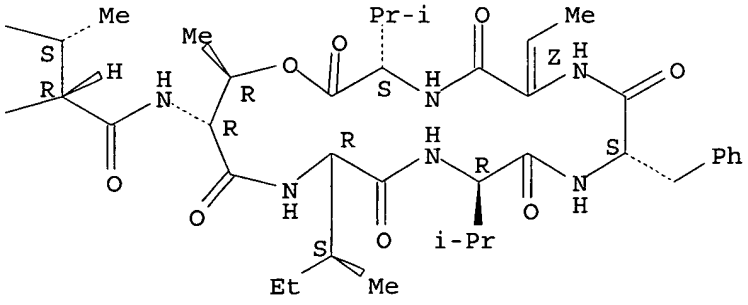
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



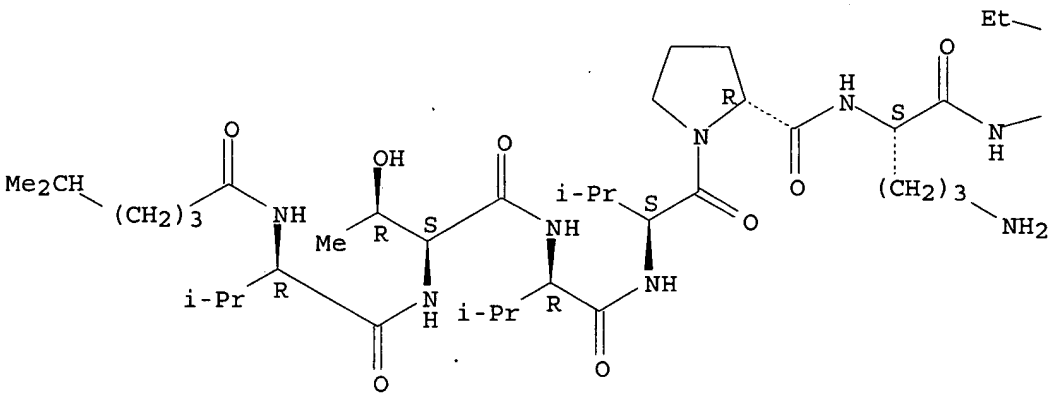
PAGE 1-B



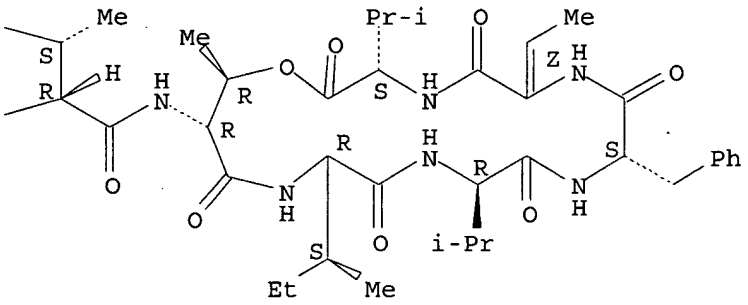
RN 354112-37-1 HCAPLUS
CN Kahalalide F, 3-D-valine-4-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 43 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:755009 HCAPLUS
DOCUMENT NUMBER: 136:79394
TITLE: Chemical and enzymatic stability of a cyclic depsipeptide, the novel, marine-derived, anti-cancer agent kahalalide F
AUTHOR(S): Sparidans, Rolf W.; Stokvis, Ellen; Jimeno, Jose M.; Lopez-Lazaro, Luis; Schellens, Jan H. M.; Beijnen, Jos H.
CORPORATE SOURCE: Faculty of Pharmacy, Department of Biomedical Analysis, Division of Drug Toxicology, Utrecht University, Utrecht, 3584 CA, Neth.
SOURCE: Anti-Cancer Drugs (2001), 12(7), 575-582
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kahalalide F is a cyclic depsipeptide isolated from the Hawaiian mollusk Elysia rufescens. This compound is under present phase I clin. investigation as an anti-tumor drug. The role of possible metabolic reactions of this drug in (pre-)clin. investigations has not yet been explored. The first results for kahalalide F in this field of research are given in this paper. The chemical degradation of kahalalide F was

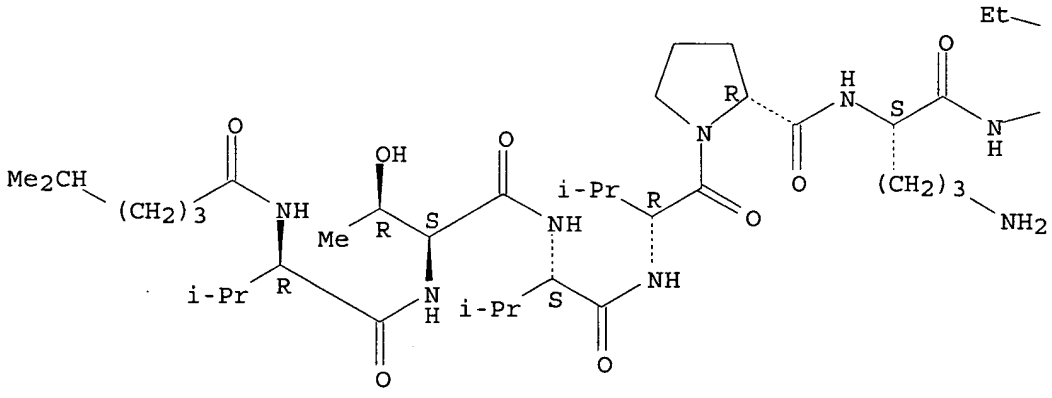
investigated under acid, neutral and alkaline conditions using high-performance liquid chromatog. with UV detection. The half-lives at 80° were 1.1, 20 and 8.6 h at pH 0, 1 and 7, resp. At 26° and pH 11, the half-life was 1.65 h. At pH 7 and 11, only one reaction product of kahalalide F was observed, kahalalide G, the hydrolyzed lactone product of kahalalide F. At pH 0 and 1, addnl. reaction products emerged. Metabolic conversion of kahalalide F was tested in vitro using three different enzyme systems based on pooled human microsomes, pooled human plasma and uridine 5'-diphosphoglucuronyl transferase, resp. The incubated samples were analyzed using the same chromatog. technique as for the degradation samples. Biotransformations were not observed under these conditions and, therefore, it is concluded that kahalalide F is a metabolically stable drug.

IT 149204-42-2, Kahalalide F
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(chemical and enzymic stability of a cyclic depsipeptide, the novel, marine-derived, anti-cancer agent kahalalide F)

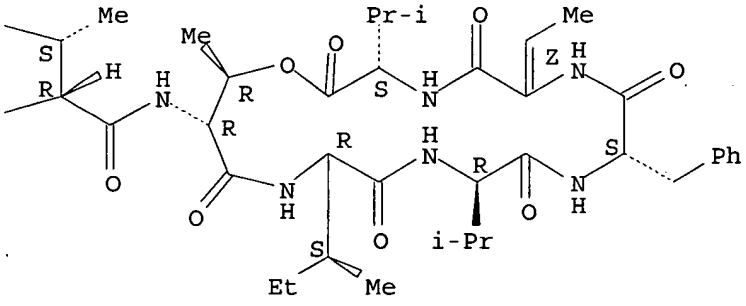
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 44 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:706055 HCAPLUS
DOCUMENT NUMBER: 136:406817
TITLE: Compatibility and stability of the investigational polypeptide marine anticancer agent kahalalide F in infusion devices
AUTHOR(S): Nuijen, Bastiaan; Bouma, Marjan; Manada, Consuelo; Jimeno, Jose M.; Lazaro, Luis L.; Bult, Auke; Beijnen, Jos H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Investigational New Drugs (2001), 19(4), 273-281
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

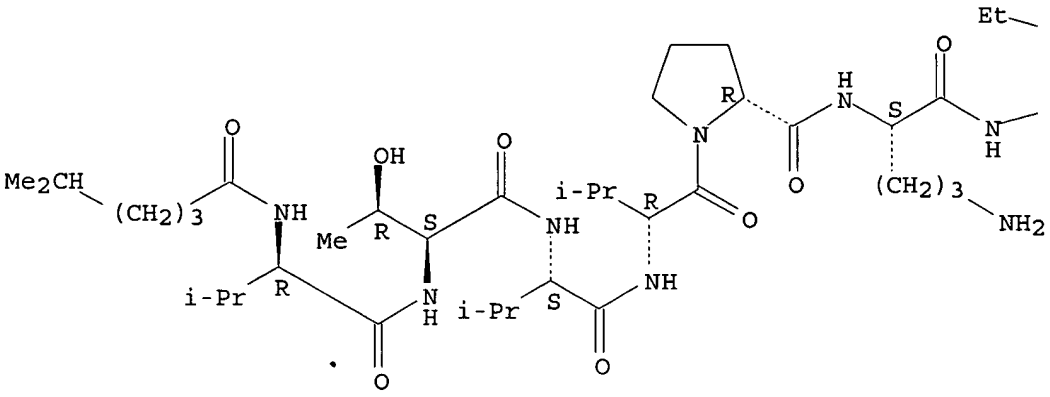
AB Kahalalide F is a novel marine-derived antitumor agent isolated from the marine mollusk Elysia rufescens, an organism living in the seas near Hawaii. The compound has shown highly selective in vitro activity against prostate tumors and phase I trials in patients with androgen independent prostate tumors incorporating a daily times five and weekly schedule have been initiated. Kahalalide F is pharmaceutically formulated as a lyophilized product containing 150 μg active substance per dosage unit. Prior to i.v. administration it is reconstituted with a solution composed of Cremophor EL, ethanol absolute and Water for Injection (CEW, 5/5/90% volume/volume/v) with further dilution in 0.9% w/v sodium chloride for infusion.

The aim of this study was to investigate the compatibility and stability of kahalalide F with different infusion systems prior to the start of clin. trials with the compound Due to the presence of Cremophor EL in the infusion solution, leaching of diethylhexyl phthalate (DEHP) from polyvinyl chloride infusion containers (PVC, Add-a-Flex) was found. Loss of kahalalide F as a consequence of sorption to contact surfaces was shown with an infusion container composed of low d. polyethylene (LD-PE, Miniflac). We conclude that kahalalide F must be administered in a 3-h infusion in concns. of 0.5 μg/mL to 14.7 μg/mL using an administration set consisting of a glass container and a low-extrables, DEHP-free extension set. Kahalalide F 150 μg/vial powder for infusion reconstituted with 5/5/90% volume/volume/v CEW is stable in the original container for at least 24 h at room temperature (+20-25°) and ambient light conditions. Infusion solns. stored in glass infusion containers at either room temperature (+20-25°, in the dark) or refrigerated conditions (+2-8°, in the dark) are stable for at least 5 days after preparation

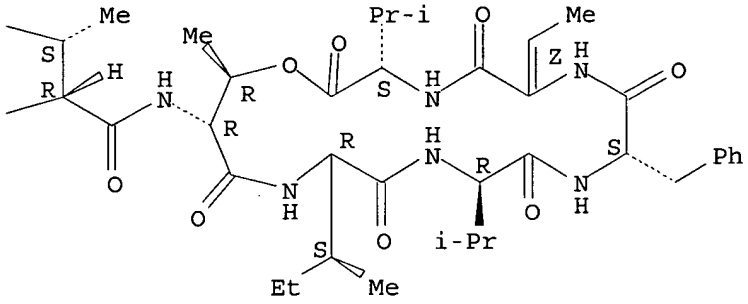
IT 149204-42-2, Kahalalide F
RL: DEV (Device component use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compatibility and stability of investigational polypeptide marine anticancer agent kahalalide F in infusion devices)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 45 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:688206 HCAPLUS
DOCUMENT NUMBER: 136:79361
TITLE: Evaluation of the use of in vitro methodologies as tools for screening new compounds for potential in vitro toxicity
AUTHOR(S): Luber-Narod, J.; Smith, B.; Grant, W.; Jimeno, J. M.; Lopez-Lazaro, L.; Faircloth, G. T.
CORPORATE SOURCE: PharmaMar USA, Inc., Cambridge, MA, 02139, USA
SOURCE: Toxicology in Vitro (2001), 15(4/5), 571-577
CODEN: TIVIEQ; ISSN: 0887-2333
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The use of in vitro methods as a safety toxicol. screen was evaluated with well-studied standard chemotherapeutic agents. Using the MTS assay (CellTiter 96 aqueous), 5-fluorouracil was found to exhibit myelocytotoxicity only. There was no cytotoxicity to liver, kidney and heart cells, except at very high concns. ET-743 was found to show hepatocytotoxicity, skeletal muscle cytotoxicity, and myelocytotoxicity and, at somewhat higher concns., nephrocytotoxicity and cardiocytotoxicity. A combination of techniques was used to measure neurotoxicity. LDH assay (CytoTox 96) and MTS assay

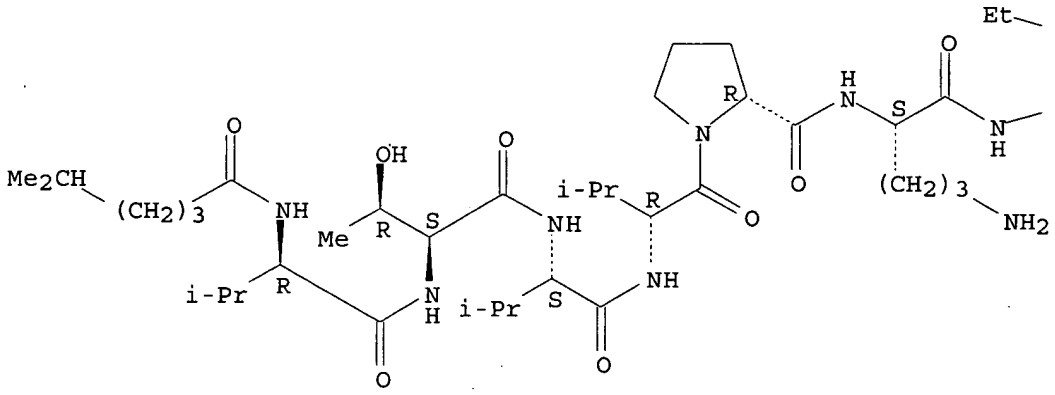
led to comparable results. These techniques determined that ET-743 is selectively cytotoxic to brain glia yet, to some extent, spares neurons. The results obtained agreed well with clin. findings of several known drugs tested.

IT 149204-42-2, Kahalalide f
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of use of in vitro methodologies as tools for screening new compds. for potential in vitro toxicity)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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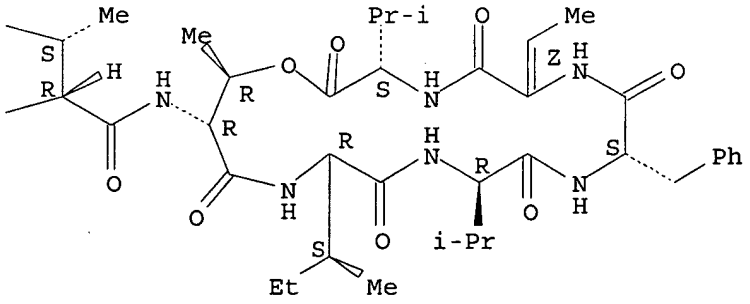

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L12 ANSWER 46 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:648439 HCAPLUS
DOCUMENT NUMBER: 136:374779
TITLE: In vitro hemolysis and buffer capacity studies with the novel marine anticancer agent kahalalide F and its reconstitution vehicle Cremophor EL/ethanol
AUTHOR(S): Nuijen, Bastiaan; Bouma, Marjan; Manada, Consuelo; Jimeno, Jose M.; Bult, Aune; Beijnen, Jos H.

CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, 1066EC, Neth.
SOURCE: PDA Journal of Pharmaceutical Science and Technology (2001), 55(4), 223-229
CODEN: JPHTEU; ISSN: 1076-397X
PUBLISHER: PDA, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

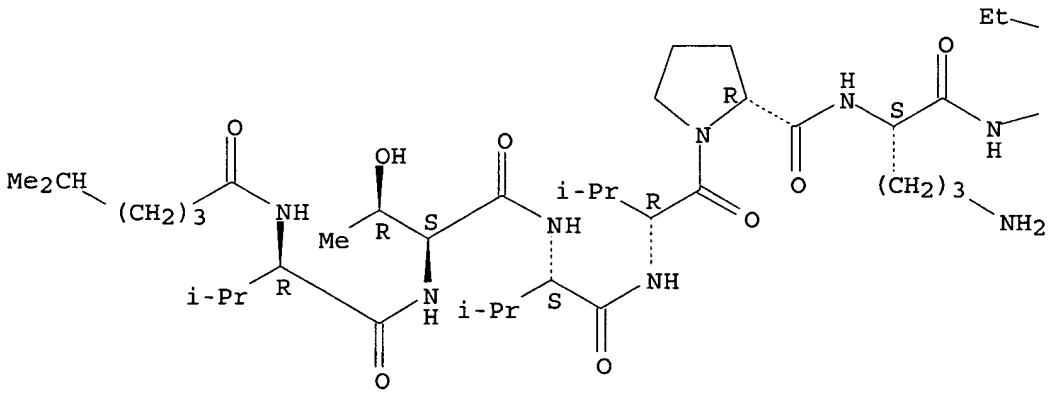
AB An in vitro biocompatibility study was performed with the pharmaceutical formulation of the investigational, marine-derived anticancer agent kahalalide F developed for early clin. studies. The pharmaceutical formulation consists of a lyophilized product containing 150 μg kahalalide F, 3 mg citric acid, 3 mg polysorbate 80, and 150 mg of sucrose per dosage unit, to be reconstituted with 3 mL of a mixture composed of Cremophor EL, ethanol, and water (5/5/90% volume/volume/v), resulting in a solution of pH 3 and
to be further diluted in normal saline for infusion. The reconstituted product, infusion solns., and Cremophor/ethanol (CE) vehicle were tested for hemolytic potential and buffer capacity. No significant hemolysis due to the kahalalide F formulation as well as the CE vehicle was found using both a static and dynamic test model. FB-ratio's (ratio of formulation solution (F) and volume of blood simulant (B) necessary to maintain physiol. pH) as a measure of the buffer capacity of the kahalalide F infusion solns. examined indicated that no vascular irritation due to pH effects is expected in the intended administration schedule in the forthcoming Phase I study.

IT 149204-42-2, Kahalalide F
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bin vitro hemolysis and buffer capacity studies with marine anticancer agent kahalalide F and its reconstitution vehicle Cremophor EL/ethanol)

RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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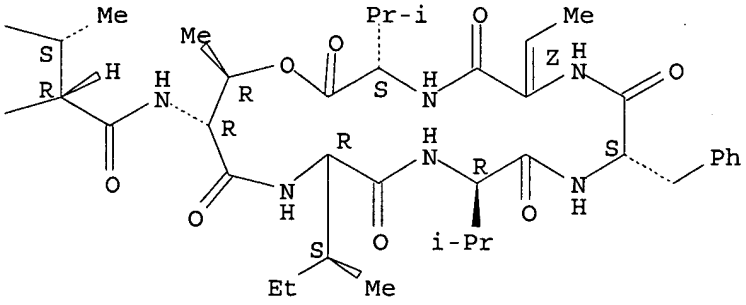

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 47 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:598019 HCAPLUS
DOCUMENT NUMBER: 135:167039
TITLE: Preparation of kahalalide compounds
INVENTOR(S): Albericio, Fernando; Giralt, Ernest; Jimenez, Jose Carlos; Lopez, Angel; Manzanares, Ignacio; Rodrigues, Ignacio; Royo, Miriam
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001058934	A2	20010816	WO 2001-GB576	20010209
WO 2001058934	A3	20020321		
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EP 1254162	A2	20021106	EP 2001-904169	20010209
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JP 2003522198	T2	20030722	JP 2001-558081	20010209
NZ 520488	A	20050324	NZ 2001-520488	20010209
AU 783542	B2	20051110	AU 2001-32086	20010209
RU 2280039	C2	20060720	RU 2002-123877	20010209
NO 2002003749	A	20021007	NO 2002-3749	20020808
BG 107020	A	20030530	BG 2002-107020	20020821
US 2004214755	A1	20041028	US 2003-182881	20030603
PRIORITY APPLN. INFO.:			GB 2000-2952 A	20000209
			WO 2001-GB576 W	20010209

OTHER SOURCE(S): MARPAT 135:167039

AB Kahalalide F and kahalalide mimic compds. having useful biol. activity were prepared The mimics differ from natural kahalalides in one or more of the following respects: at least one amino acid which is not the same as an amino acid present in the parent compound and at least one methylene group or substituent in the side chain acyl group of the parent compound is addnl. or omitted. Approx. 40 kahalalide analogs, including 5-MeHex-D-Val-Thr-Val-D-Val-D-Pro-Orn-D-allo-Ile-cyclo(D-allo-Thr-D-allo-Ile-D-Val-Phe-Etg-Val) (5-MeHex is 5-methylhexanoyl and Etg is ethylglycine residue), were prepared by the solid phase method and their cytotoxicities (IC50 values) tabulated.

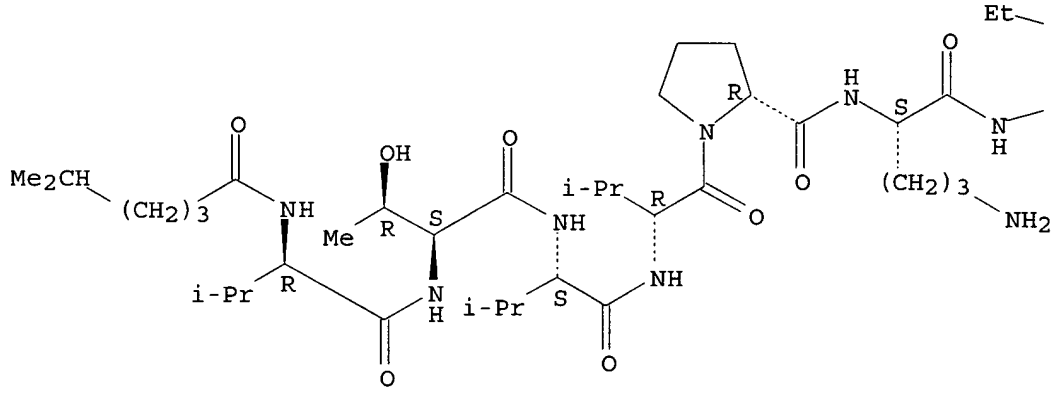
IT 353491-44-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BYP (Byproduct); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of kahalalide compds.)

RN 353491-44-8 HCAPLUS

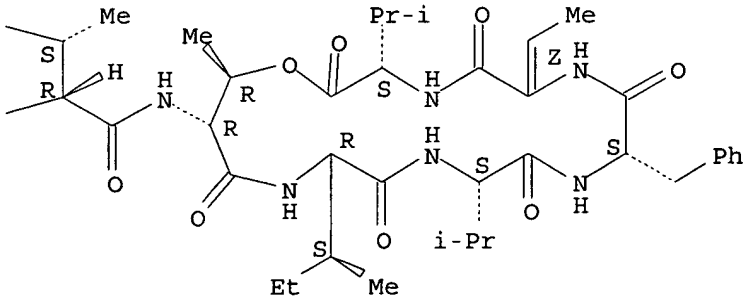
CN Kahalalide F, 10-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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353491-56-2P 353491-57-3P 353491-58-4P
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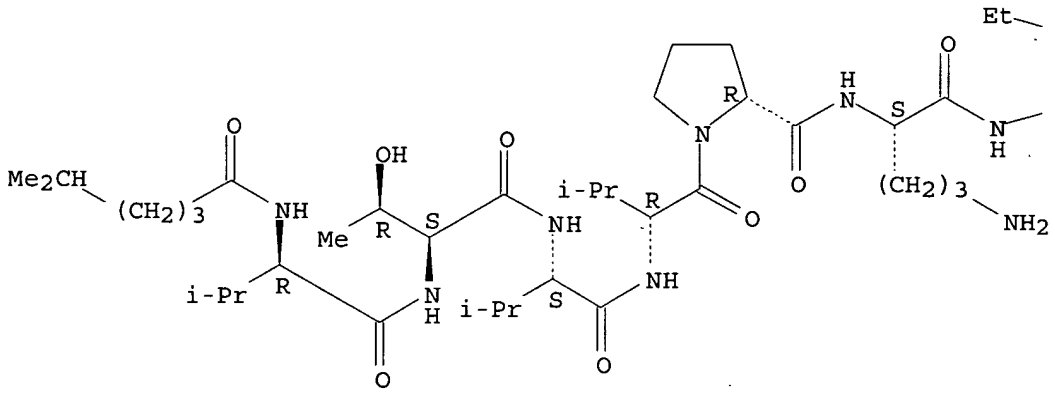
354112-37-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of kahalalide compds.)

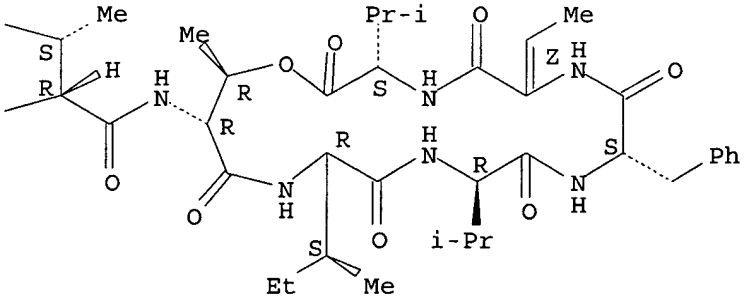
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



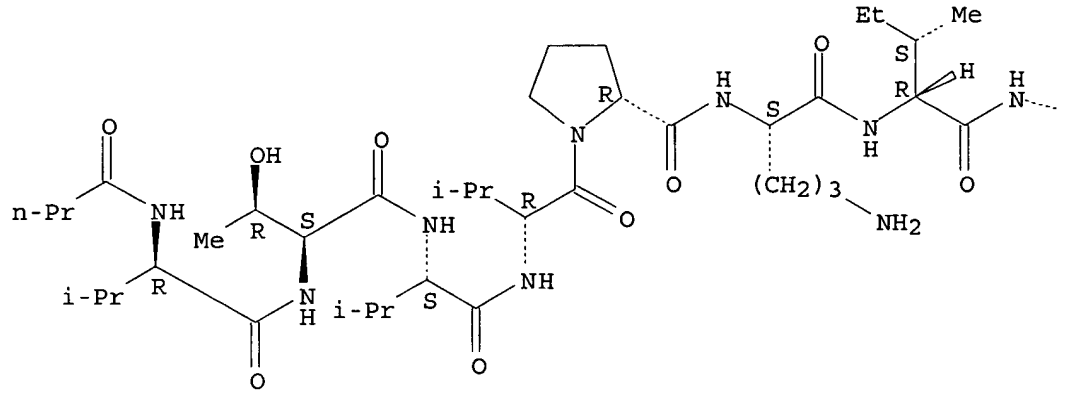
PAGE 1-B



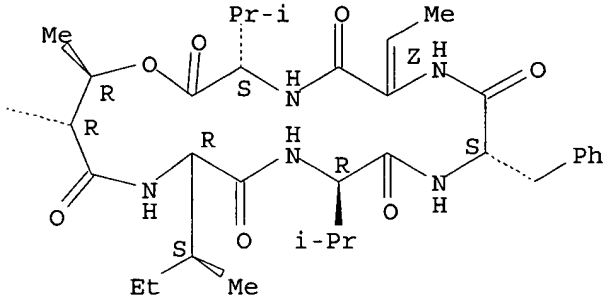
RN 353491-55-1 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxobutyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



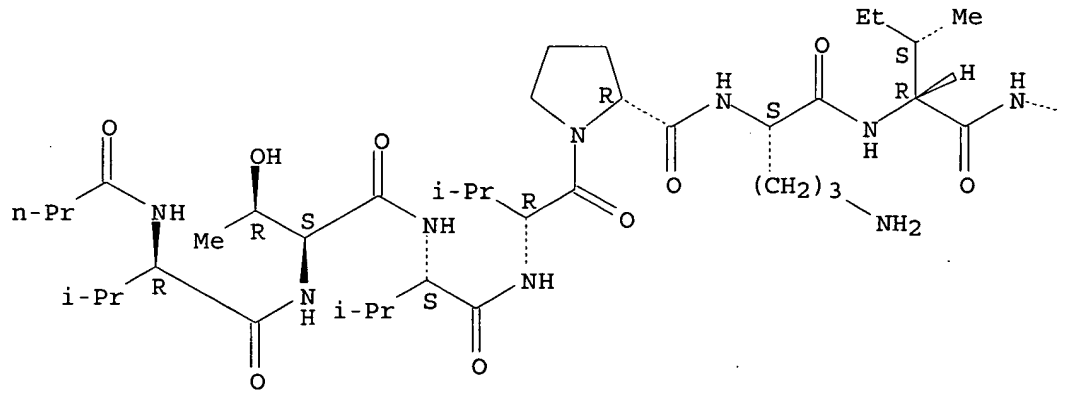
PAGE 1-B



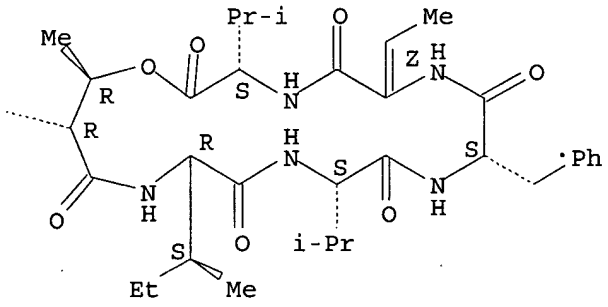
RN 353491-56-2 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxobutyl)-D-valine]-10-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



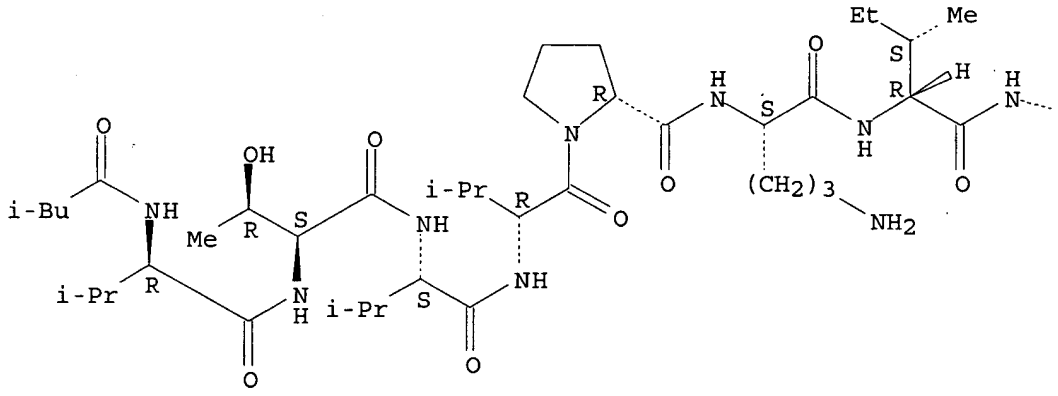
PAGE 1-B



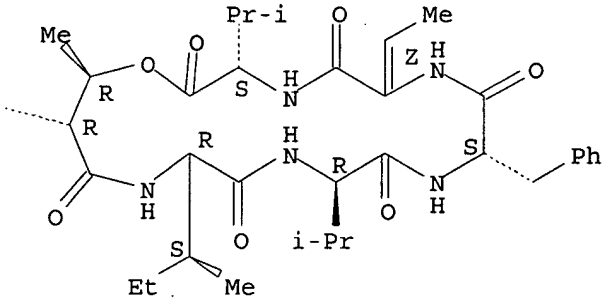
RN 353491-57-3 HCAPLUS
CN Kahalalide F, 1-[N-(3-methyl-1-oxobutyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



RN 353491-58-4 HCAPLUS
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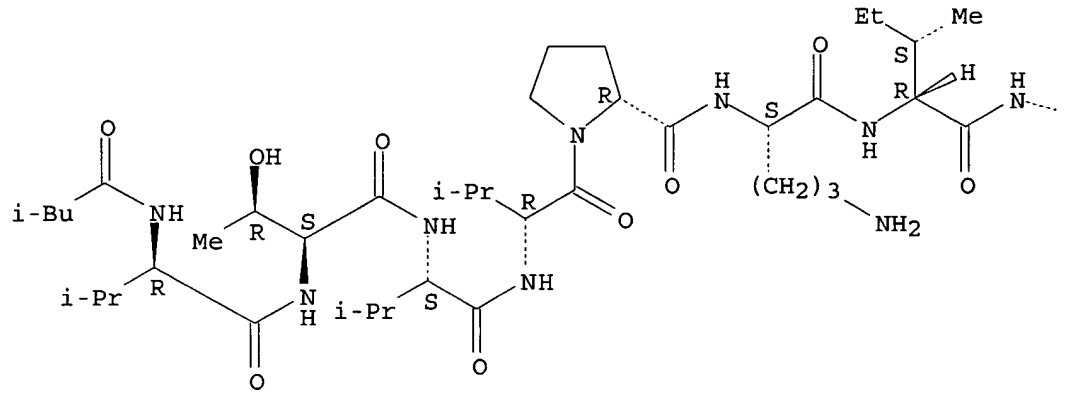
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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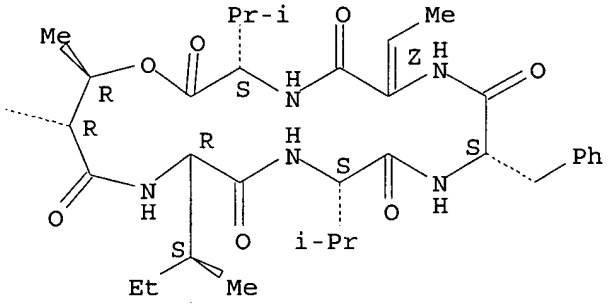
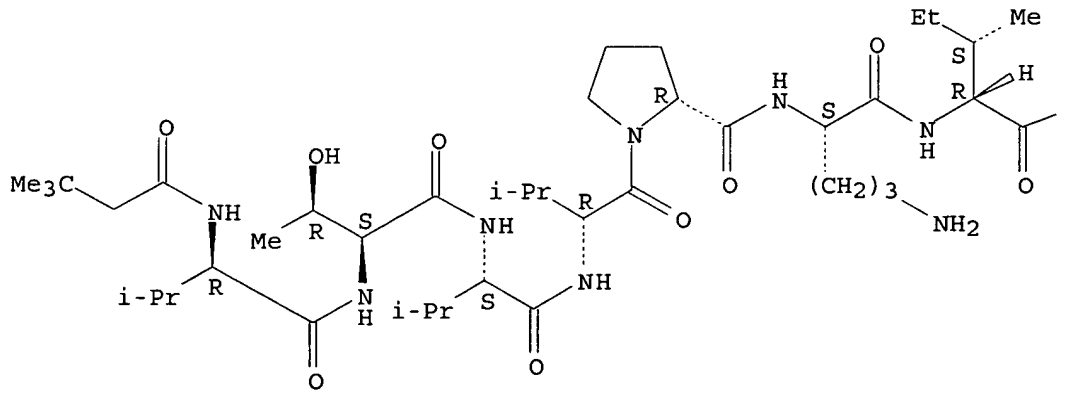


RN 353491-59-5 HCAPLUS
CN Kahalalide F, 1-[N-(3,3-dimethyl-1-oxobutyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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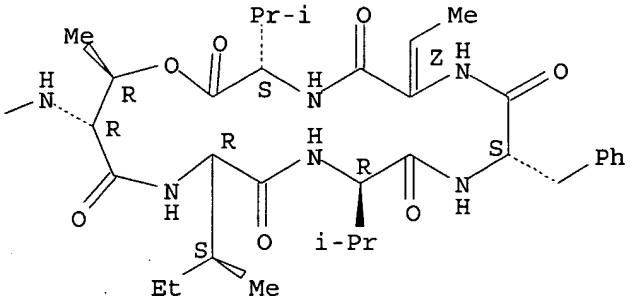
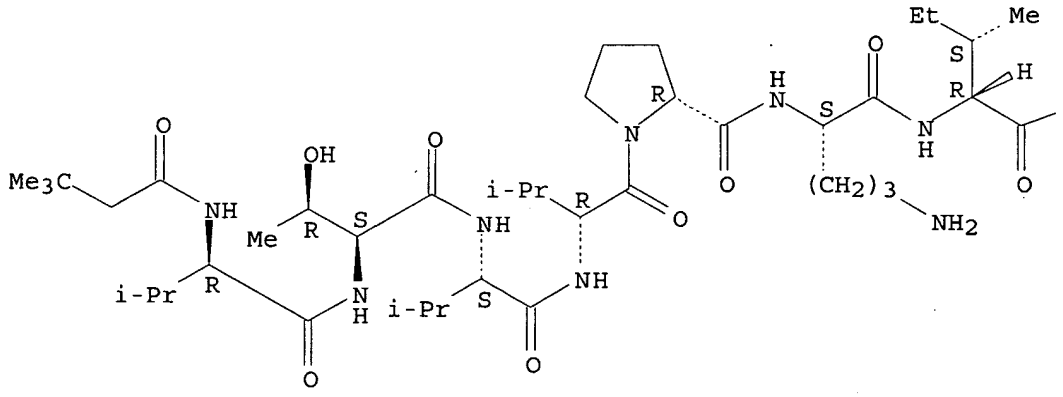


RN 353491-60-8 HCAPLUS
CN Kahalalide F, 1-[N-(3,3-dimethyl-1-oxobutyl)-D-valine]-10-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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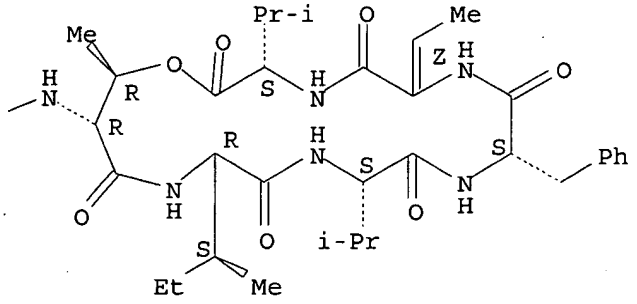
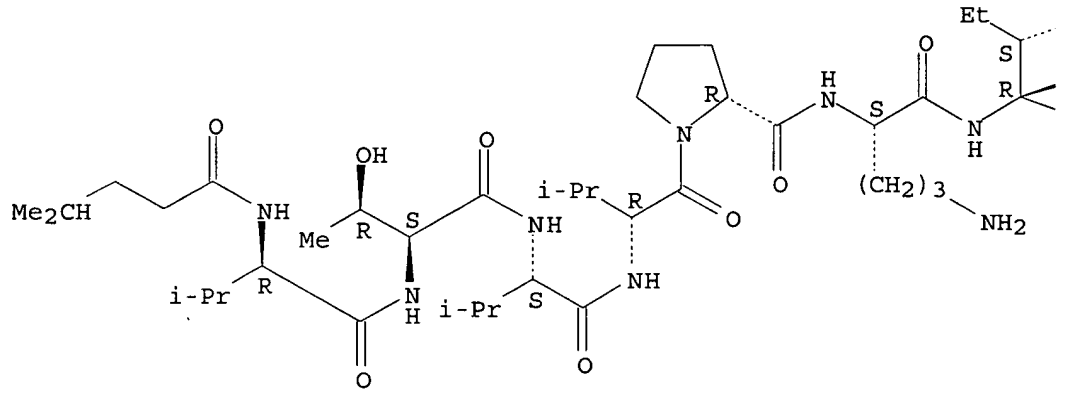


RN 353491-61-9 HCAPLUS

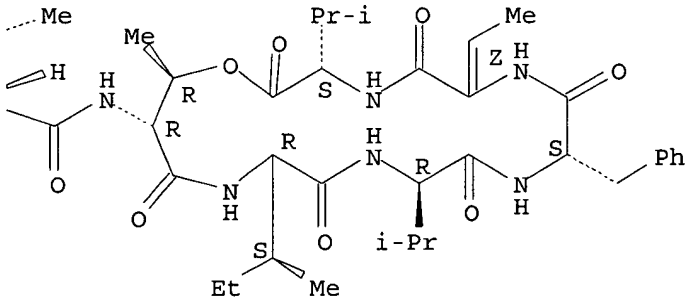
CN Kahalalide F, 1-[N-(4-methyl-1-oxopentyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



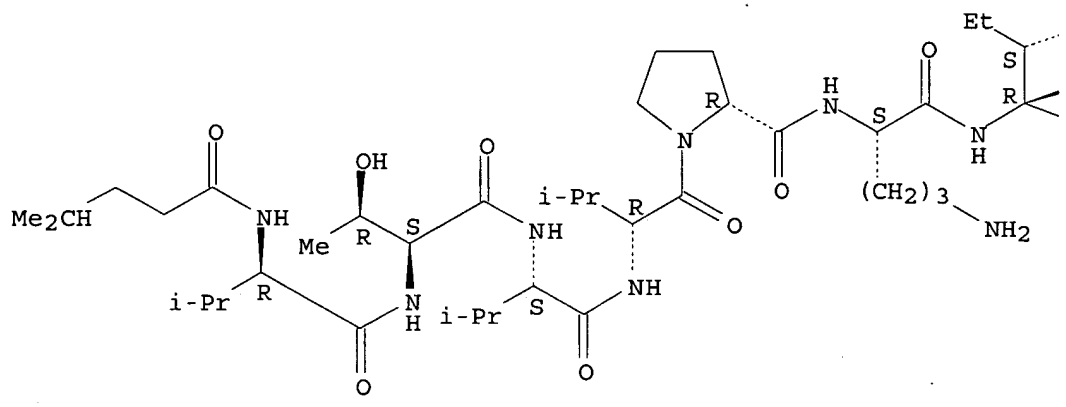
PAGE 1-B



RN 353491-62-0 HCAPLUS
CN Kahalalide F, 1-[N-(4-methyl-1-oxopentyl)-D-valine]-10-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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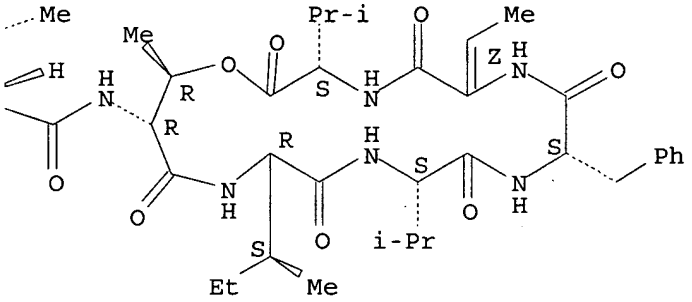
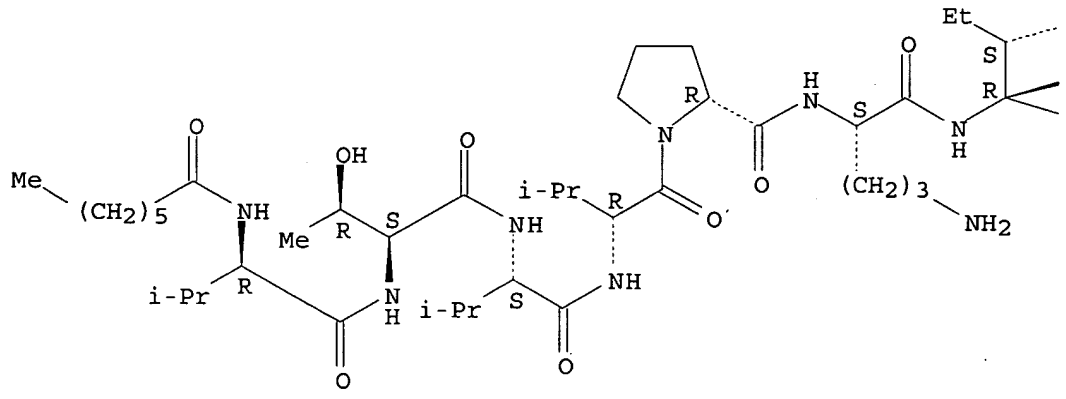


RN 353491-63-1 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxoheptyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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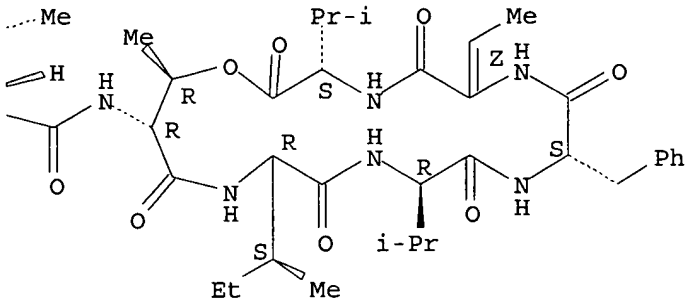
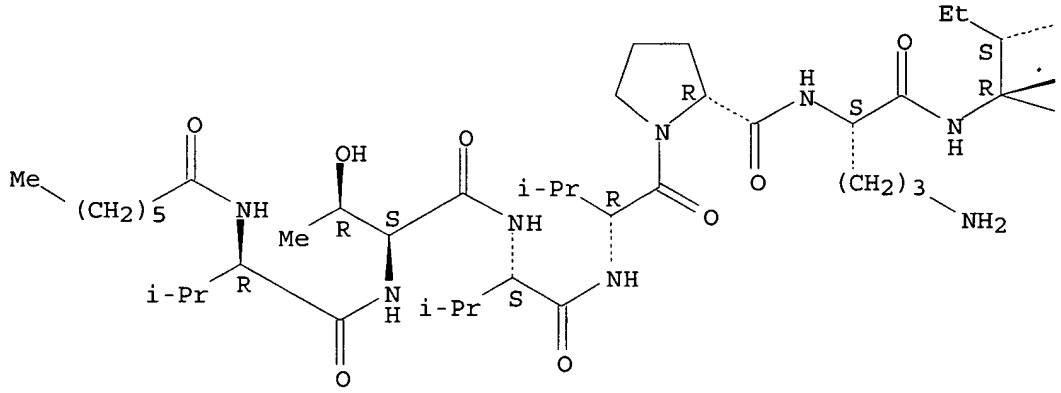


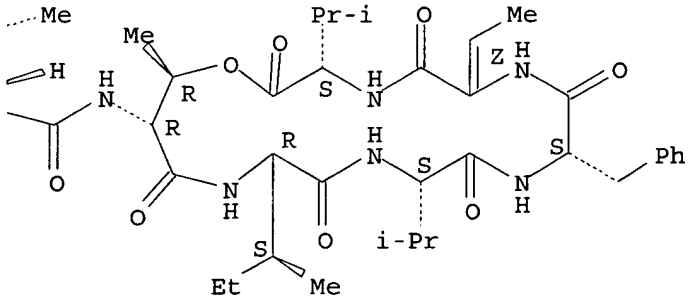
RN 353491-64-2 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxoheptyl)-D-valine]-10-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

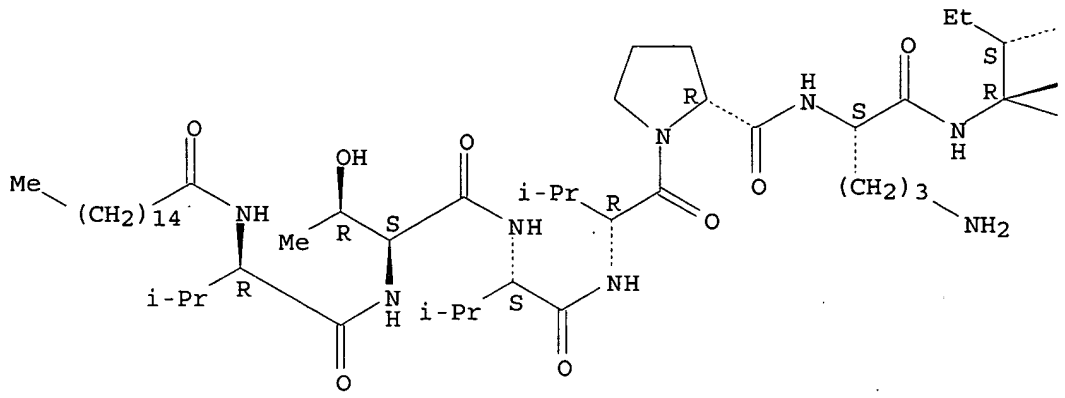


RN 353491-65-3 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxohexadecyl)-D-valine]- (9CI) (CA INDEX NAME)

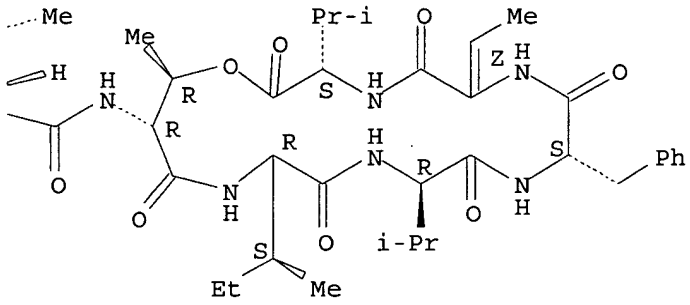
Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



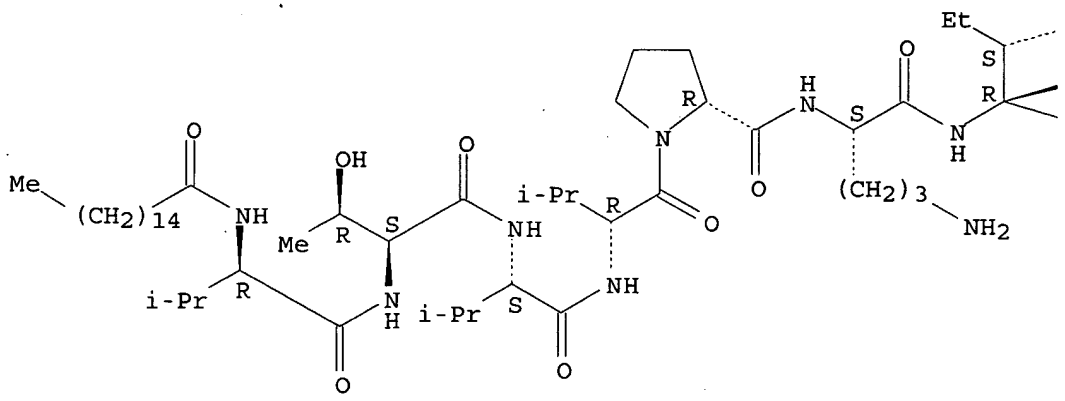
PAGE 1-B



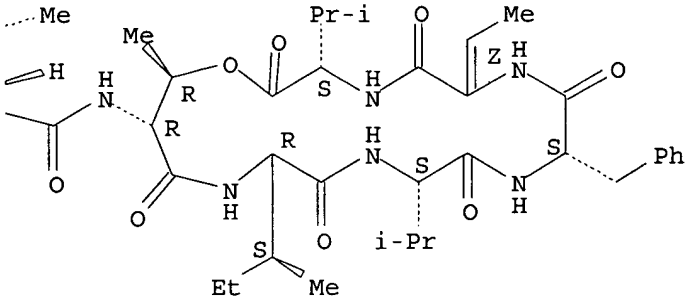
RN 353491-66-4 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxohexadecyl)-D-valine]-10-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



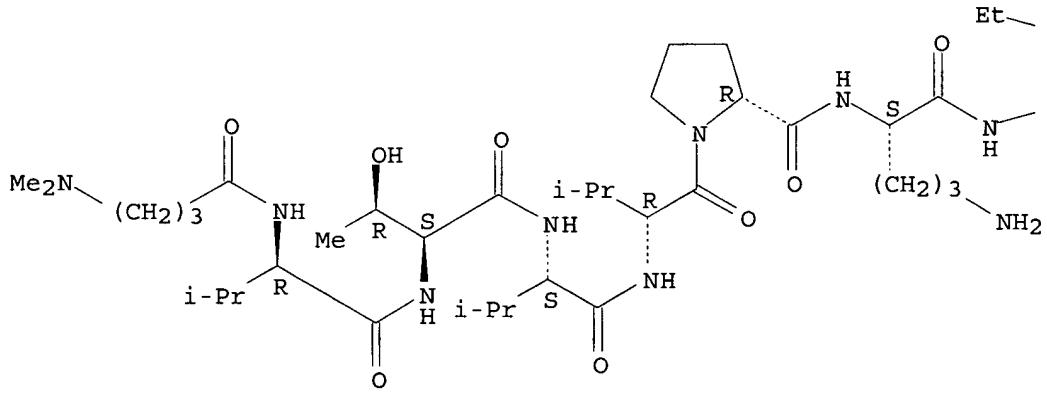
PAGE 1-B



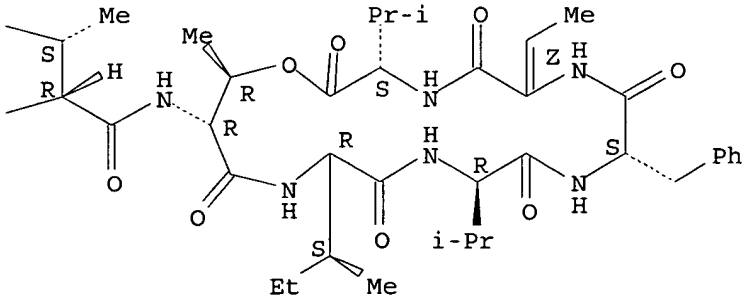
RN 353491-67-5 HCAPLUS
CN Kahalalide F, 1-[N-[4-(dimethylamino)-1-oxobutyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

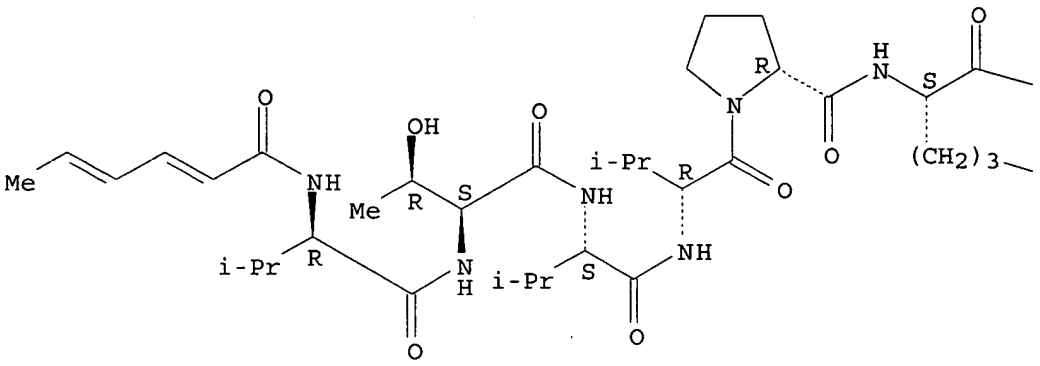


RN 353491-68-6 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxo-2,4-hexadienyl)-D-valine]- (9CI) (CA INDEX

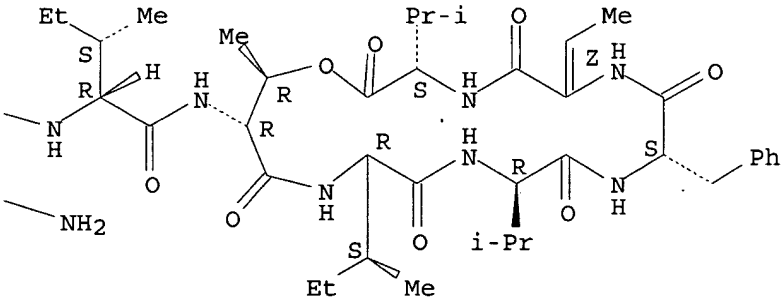
NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



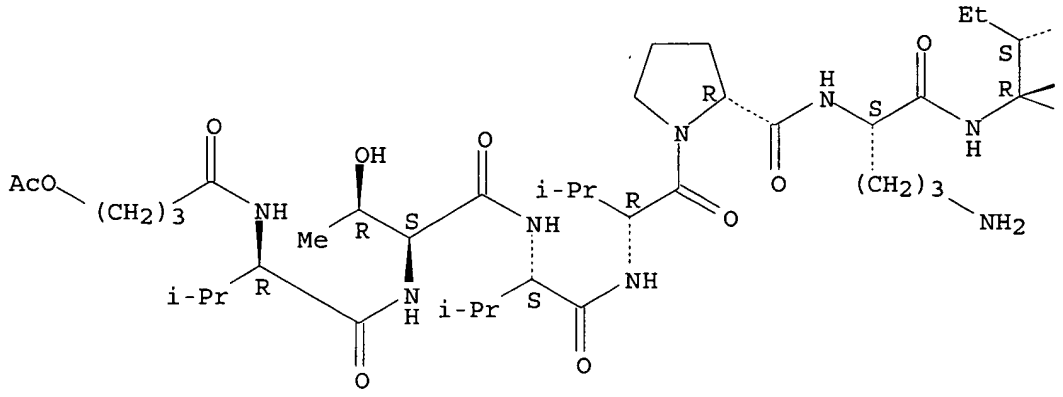
PAGE 1-B



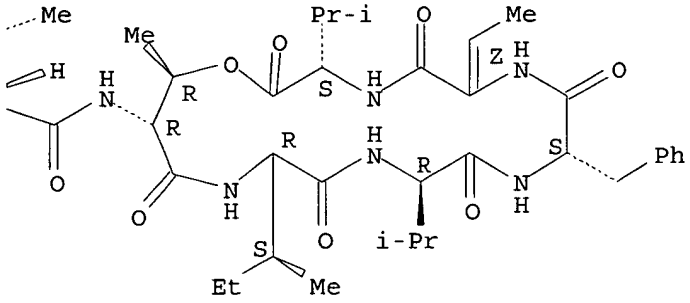
RN 353491-69-7 HCAPLUS
CN Kahalalide F, 1-[N-[4-(acetyloxy)-1-oxobutyl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



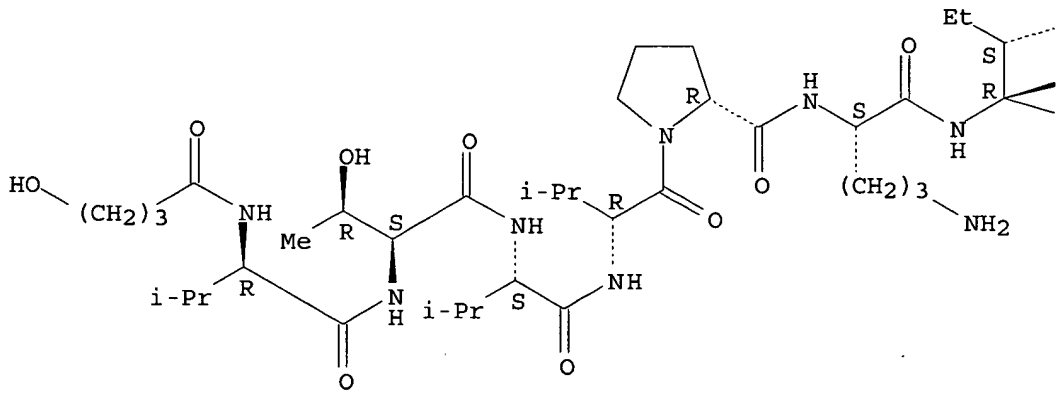
PAGE 1-B



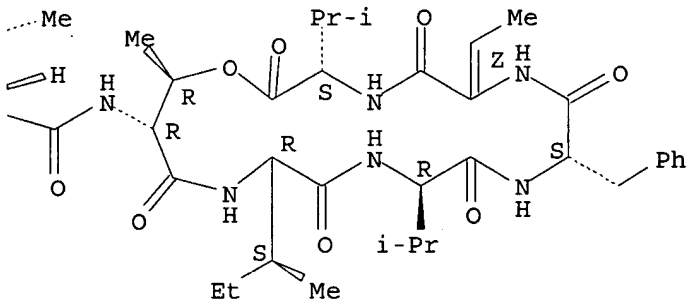
RN 353491-70-0 HCAPLUS
CN Kahalalide F, 1-[N-(4-hydroxy-1-oxobutyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



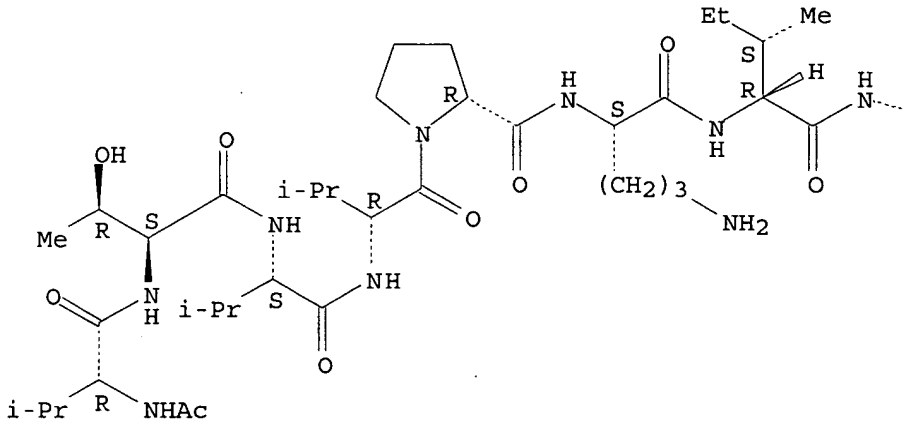
PAGE 1-B



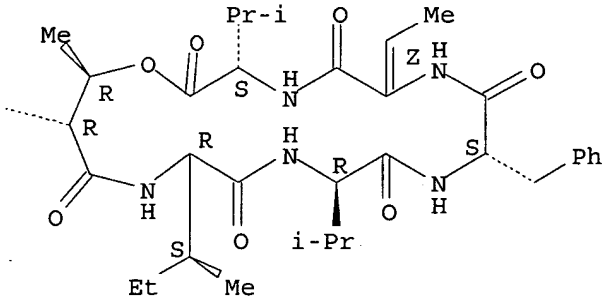
RN 353491-71-1 HCAPLUS
CN Kahalalide F, 1-(N-acetyl-D-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



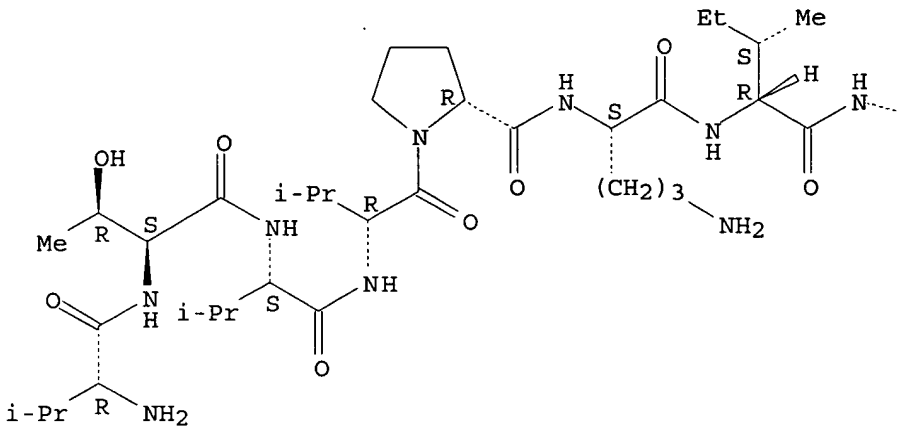
PAGE 1-B



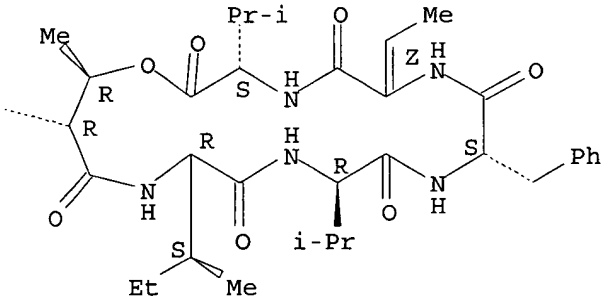
RN 353491-72-2 HCAPLUS
CN Kahalalide F, 1-D-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



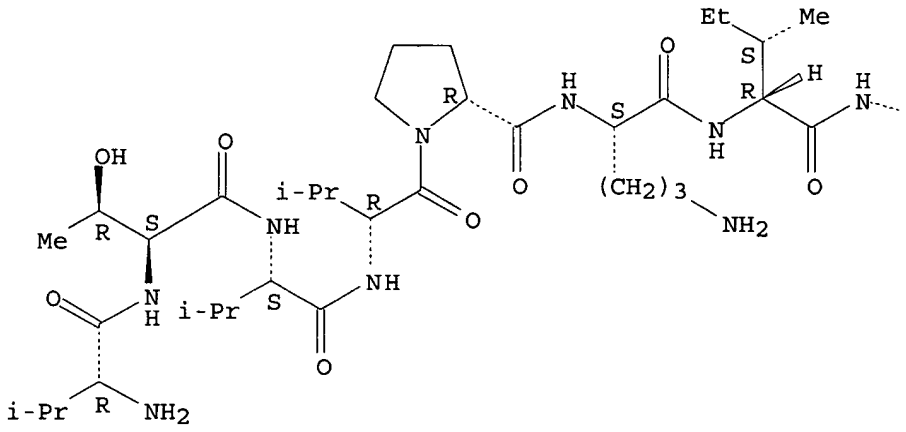
RN 353491-73-3 HCAPLUS
CN Kahalalide F, 1-D-valine-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

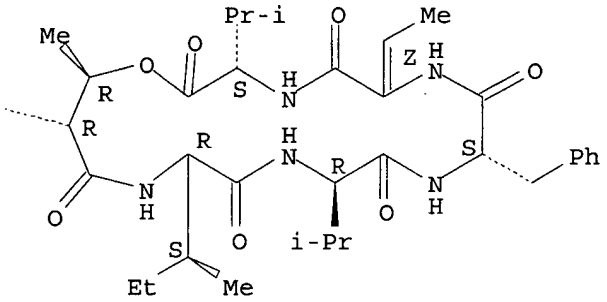
CRN 353491-72-2
CMF C68 H112 N14 O15

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

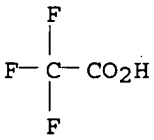


PAGE 1-B



CM 2

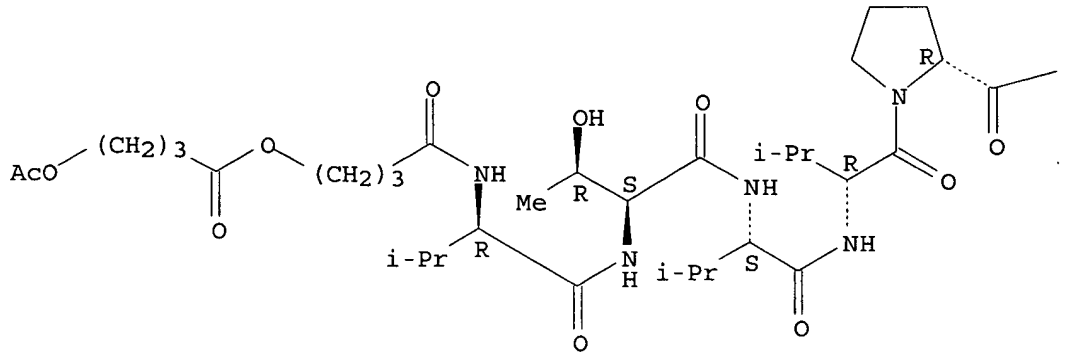
CRN 76-05-1
CMF C2 H F3 O2



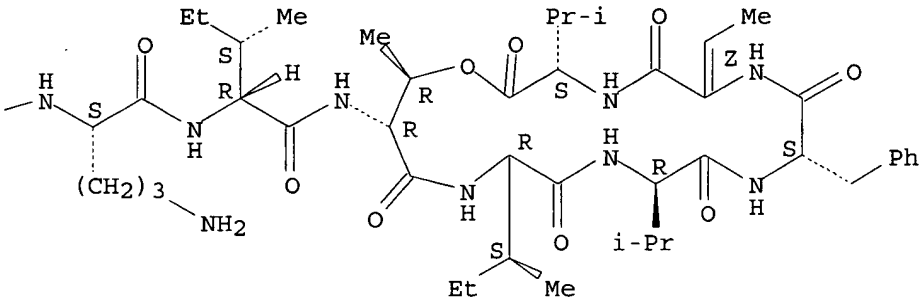
RN 353491-74-4 HCAPLUS
CN Kahalalide F, 1-[N-[4-[4-(acetyloxy)-1-oxobutoxy]-1-oxobutyl]-D-valine]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



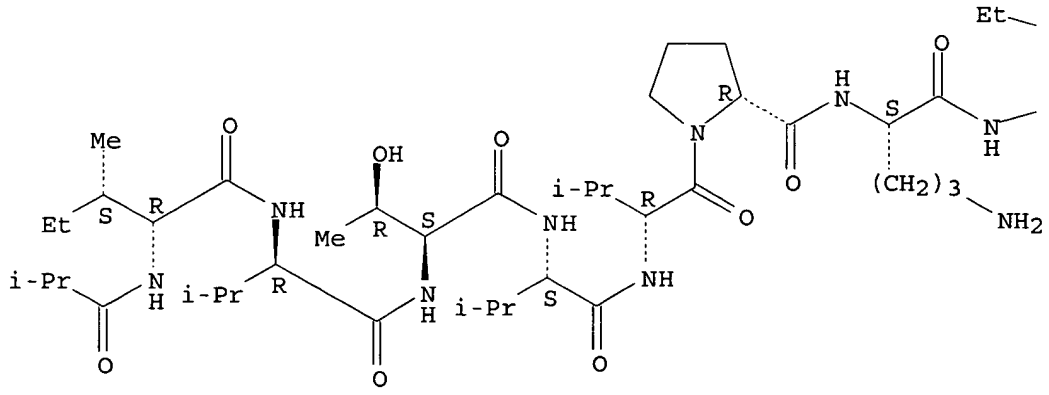
PAGE 1-B



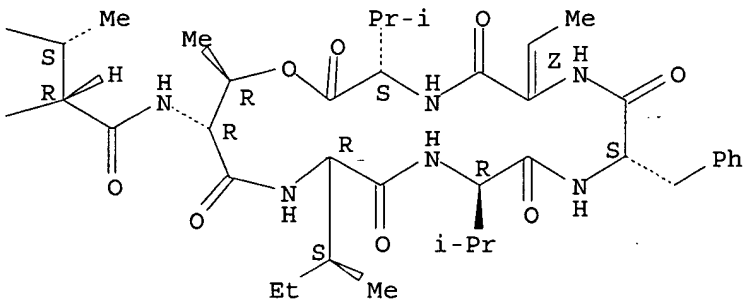
RN 353491-75-5 HCAPLUS
CN Kahalalide F, 1-[N-(2-methyl-1-oxopropyl)-D-alloisoleucyl-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



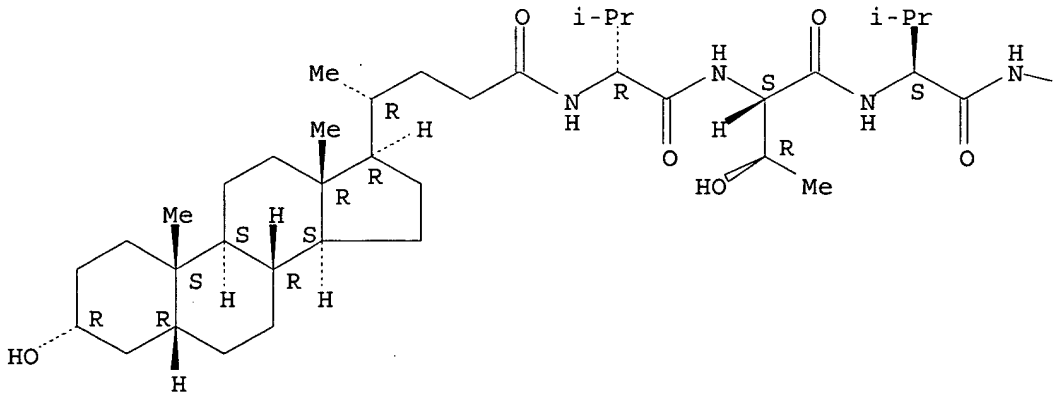
PAGE 1-B



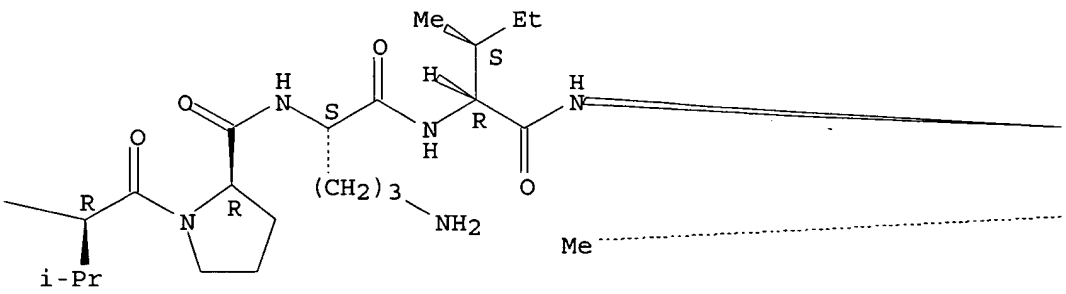
RN 353491-76-6 HCAPLUS
CN Kahalalide F, 1-[N-[(3α,5β)-3-hydroxy-24-oxocholan-24-yl]-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

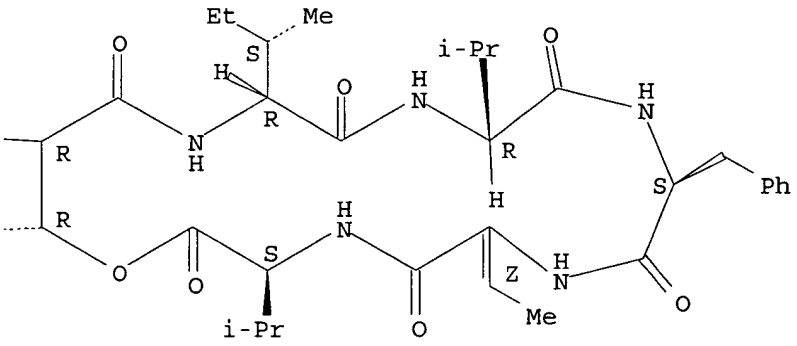
PAGE 1-A



PAGE 1-B



PAGE 1-C



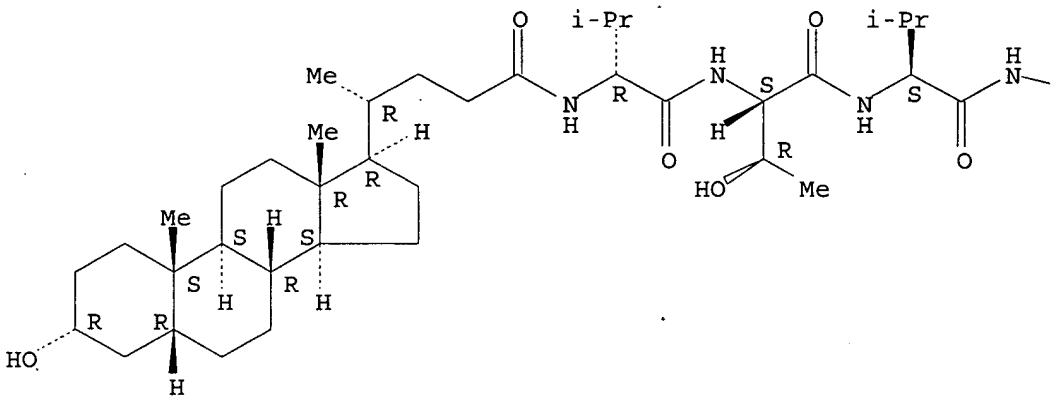
RN 353491-77-7 HCAPLUS
CN Kahalalide F, 1-[N-[(3α,5β)-3-hydroxy-24-oxocholan-24-yl]-D-valine]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

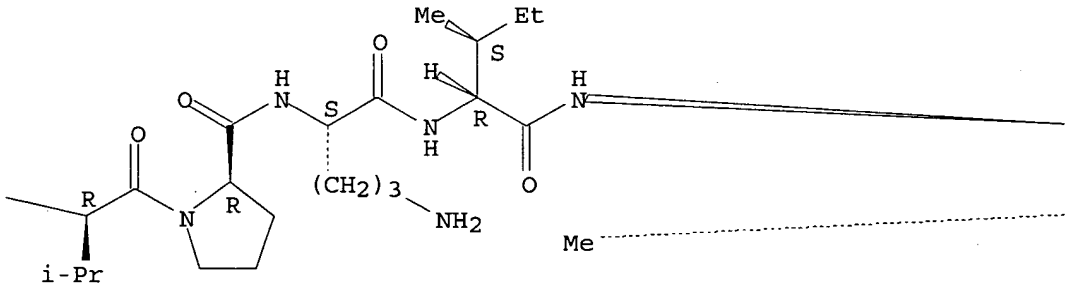
CRN 353491-76-6
CMF C92 H150 N14 O17

Absolute stereochemistry.
Double bond geometry as shown.

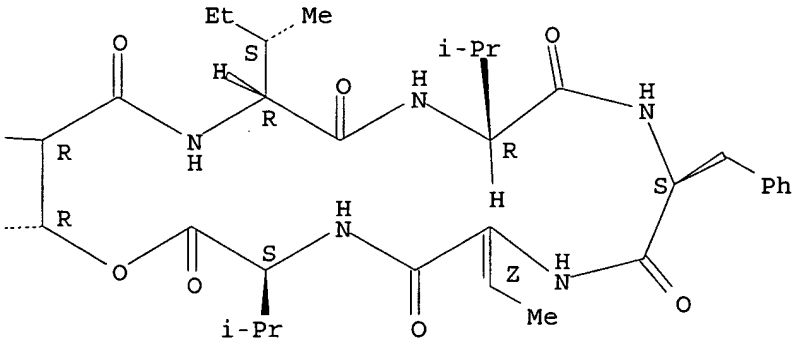
PAGE 1-A



PAGE 1-B

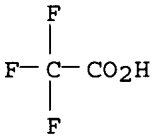


PAGE 1-C



CM 2

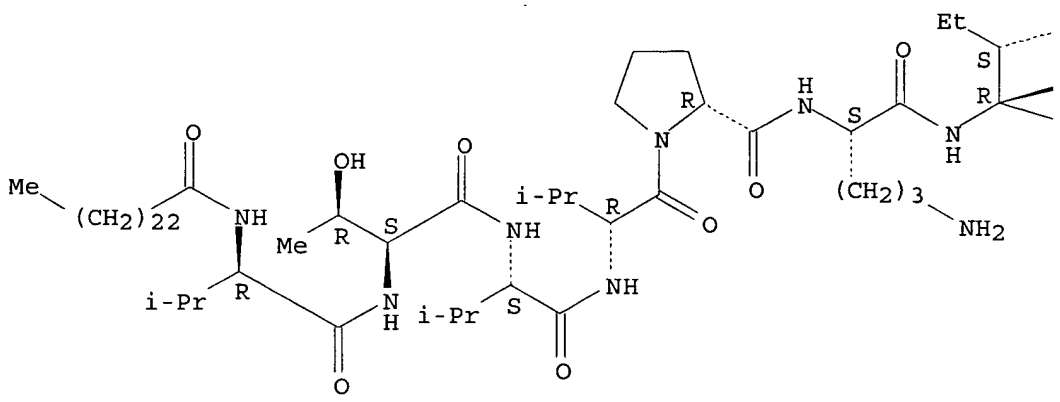
CRN 76-05-1
CMF C2 H F3 O2



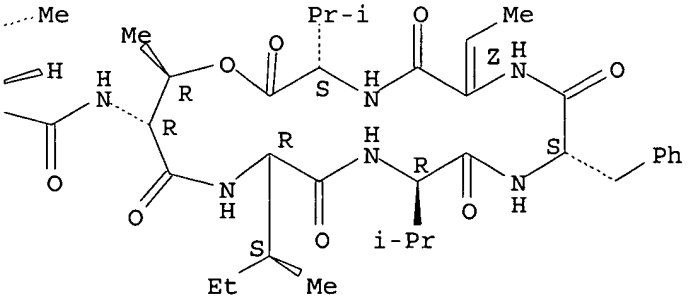
RN 353491-78-8 HCAPLUS
CN Kahalalide F, 1-[N-(1-oxotetracosyl)-D-valine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



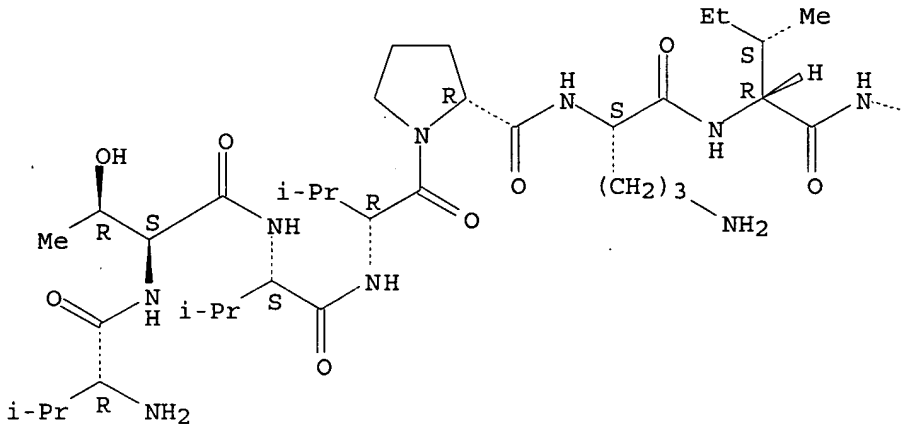
PAGE 1-B



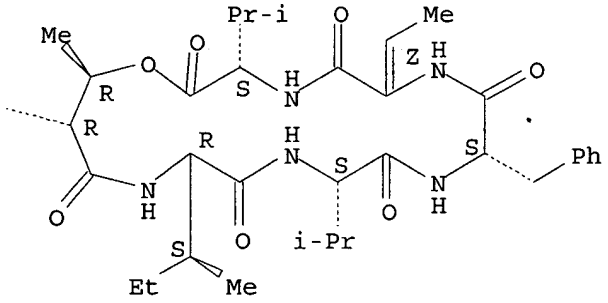
RN 353491-79-9 HCAPLUS
CN Kahalalide F, 1-D-valine-10-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



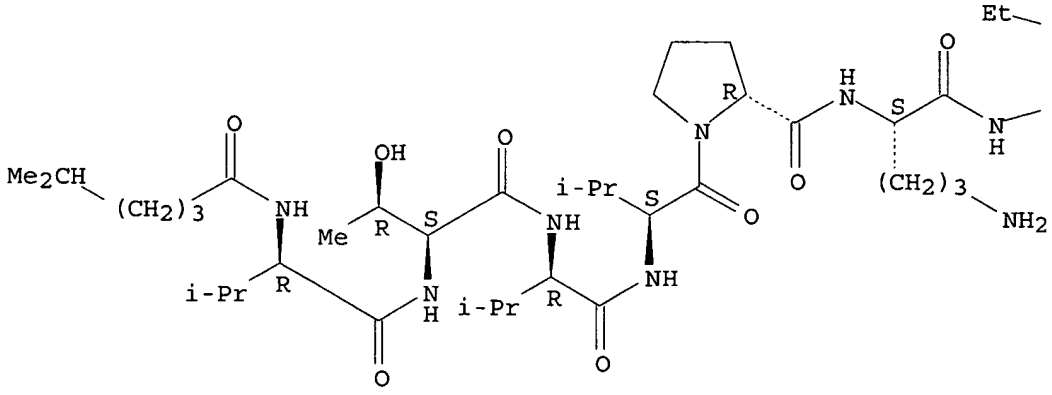
PAGE 1-B



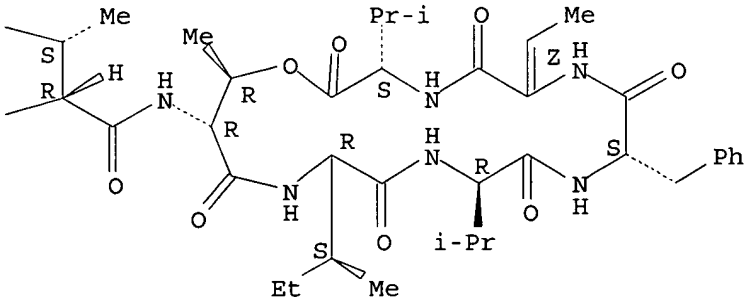
RN 354112-37-1 HCAPLUS
CN Kahalalide F, 3-D-valine-4-L-valine- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 48 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:593276 HCAPLUS
DOCUMENT NUMBER: 135:170762
TITLE: Cytotoxic and antimicrobial activities of Kahalalide F from Elysia rufescens
INVENTOR(S): Scheuer, Paul J.; Hamann, Mark T.; Gravalos, Dolores G.
PATENT ASSIGNEE(S): PharmaMar, S.A., Spain
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6274551	B1	20010814	US 1994-192569	19940203
US 6011010	A	20000104	US 1997-935073	19970925
PRIORITY APPLN. INFO.:			US 1994-192569	A1 19940203

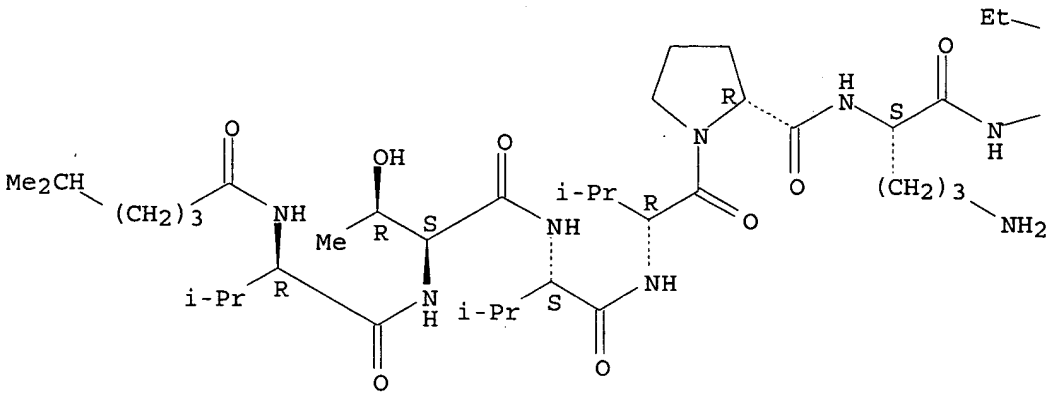
AB Kahalalide F (I) is isolated from a sacoglossan (Elysia rufescens). I may be used in the manufacture of pharmaceutical compns. or in the treatment of tumors or viral conditions. Two hundred sacoglossans (E. rufescens), were collected and extracted 3 times with EtOH. The combined exts. were then chromatographed on silica gel flash chromatog. by using hexane, hexane/EtOAc (1:1), EtOAc, EtOAc/MeOH (1:1), MeOH, MeOH/HOAc (98:2). The depsipeptides were found in the EtOAc/MeOH (1:1) fraction. Repeated RP-HPLC yielded 6 new depsipeptides, out of which I was isolated and its structure was determined

IT 149204-42-2, Kahalalide F
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(cytotoxic and antimicrobial activities of Kahalalide F from Elysia rufescens)

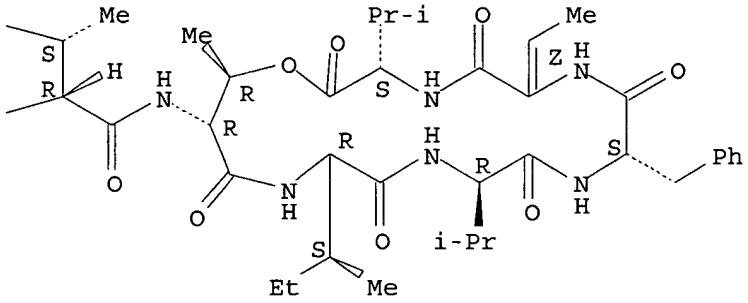
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 49 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:128631 HCAPLUS
DOCUMENT NUMBER: 132:290934
TITLE: Marine natural products as antituberculosis agents
AUTHOR(S): El Sayed, Khalid A.; Bartyzel, Piotr; Shen, Xiaoyu; Perry, Tony L.; Zjawiony, Jordan K.; Hamann, Mark T.
CORPORATE SOURCE: Department of Pharmacognosy, NCNPR School of Pharmacy, The University of Mississippi, MS, 38677, USA
SOURCE: Tetrahedron (2000), 56(7), 949-953
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB In an attempt to characterize addnl. structural classes that could serve as lead antituberculosis agents, 48 structurally diverse marine-derived

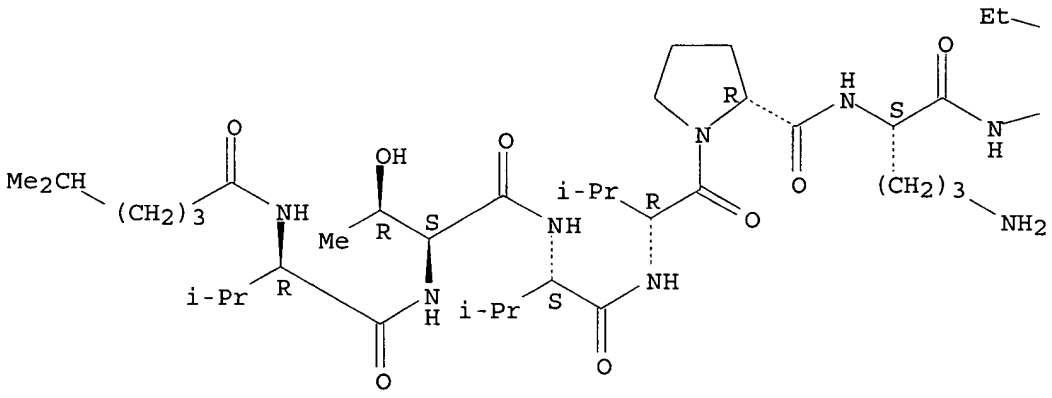
natural and semisynthetic compds. were examined for in vitro activity against Mycobacterium tuberculosis. Three new classes of compds. including C-19 hydroxy steroids [e.g. litosterol (I)], scalarin sesquiterpenoids [e.g. heteronemin (II)], and tetrabromo spirocyclohexadienylisoxazolines [e.g. 11-hydroxyaerothionin (III)] have been identified as having potential as leads for continued investigations as new antituberculosis agents. New addns. to the established antituberculosis structural classes quinone-methide and peptide are also reported.

IT 149204-42-2, Kahalalide F
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(marine natural products as antituberculosis agents)

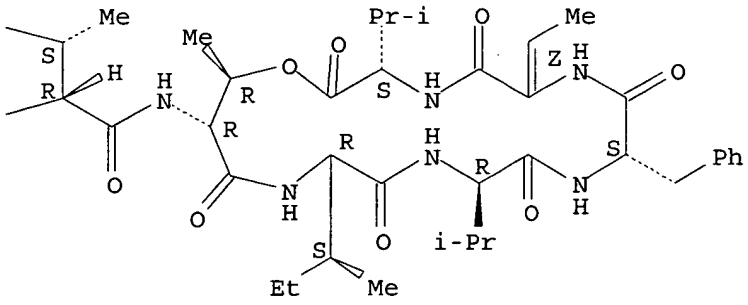
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 50 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:10614 HCAPLUS
DOCUMENT NUMBER: 132:59154

TITLE: Kahalalide F or salts of this sacoglossan peptide in treatment of tumors and viral infections in mammals
INVENTOR(S): Scheuer, Paul J.; Hamann, Mark T.; Gravalos, Dolores G.
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain
SOURCE: U.S., 5 pp., Cont. of U.S. Ser. No. 192,569.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

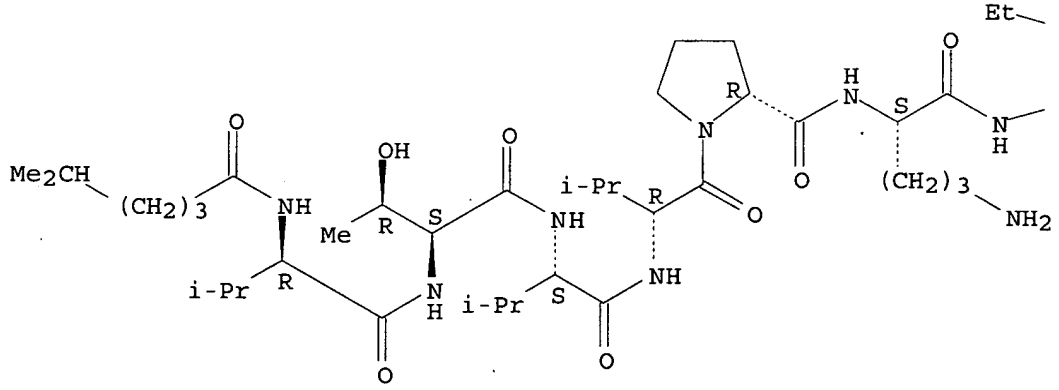
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6011010	A	20000104	US 1997-935073	19970925
US 6274551	B1	20010814	US 1994-192569	19940203
PRIORITY APPLN. INFO.:			US 1994-192569	A1 19940203

AB Kahalalide F, a peptide that may be isolated from a sacoglossan (Elysia rufescens), or a pharmaceutically acceptable salt thereof, may be used in the treatment of mammalian tumors or viral infections. Use for treatment of human lung carcinoma, human colon carcinoma, Herpes simplex and Vesicular Stomatitis viral infections in mammals is claimed.

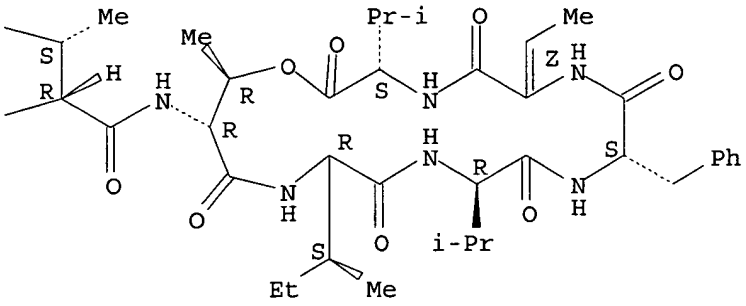
IT 149204-42-2, Kahalalide F 149204-42-2D, Kahalalide F, salts
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in treatment of human carcinomas and mammalian viral infections)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



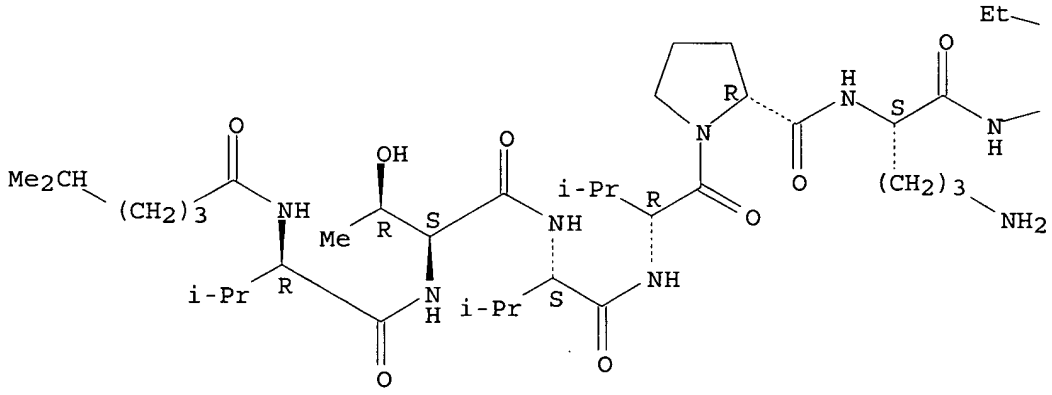
PAGE 1-B



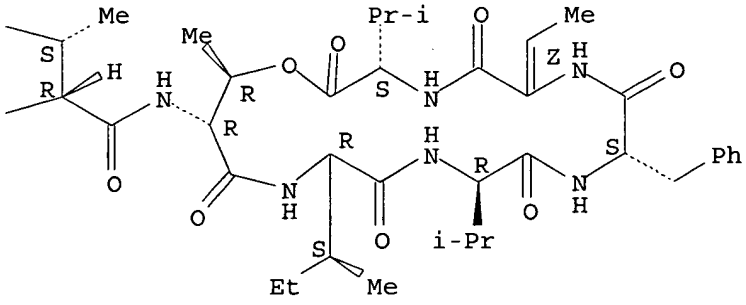
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



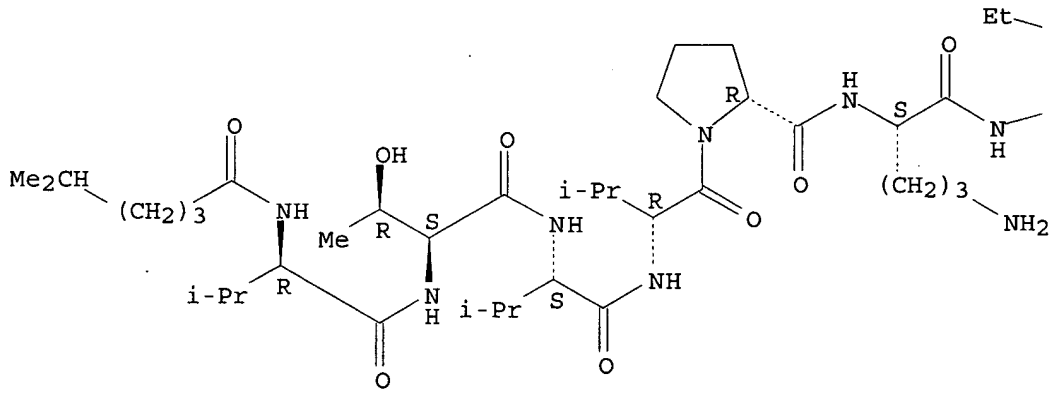
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 51 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:631977 HCAPLUS

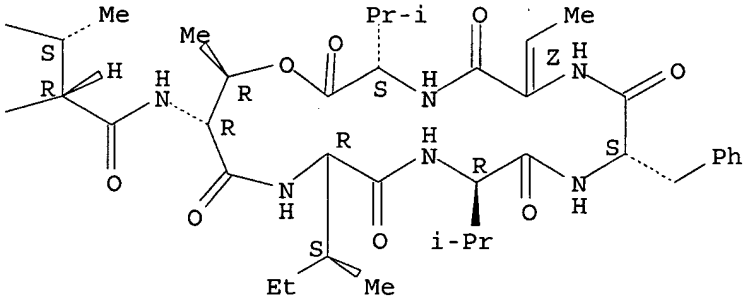
DOCUMENT NUMBER: 131:337344
TITLE: The absolute stereochemistry of kahalalide F. [Erratum to document cited in CA131:157974]
AUTHOR(S): Goetz, Gilles; Yoshida, Wesley Y.; Scheuer, Paul J.
CORPORATE SOURCE: Department of Chemistry, University of Hawaii, Honolulu, HI, 96822, USA
SOURCE: Tetrahedron (1999), 55(40), 11957
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On page vii, in the graphical abstract, L-Pro should read D-Pro.
IT 149204-42-2, Kahalalide F
RL: PRP (Properties); RCT (Reactant); RACT (Reactant or reagent)
(absolute stereochem. of kahalalide F (Erratum))
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 52 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:392419 HCAPLUS
DOCUMENT NUMBER: 131:157974
TITLE: The absolute stereochemistry of kahalalide F

AUTHOR(S): Goetz, Gilles; Yoshida, Wesley Y.; Scheuer, Paul J.
CORPORATE SOURCE: Dep. Chemistry, Univ. Hawaii, Honolulu, HI, 96822, USA
SOURCE: Tetrahedron (1999), 55(25), 7739-7746
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

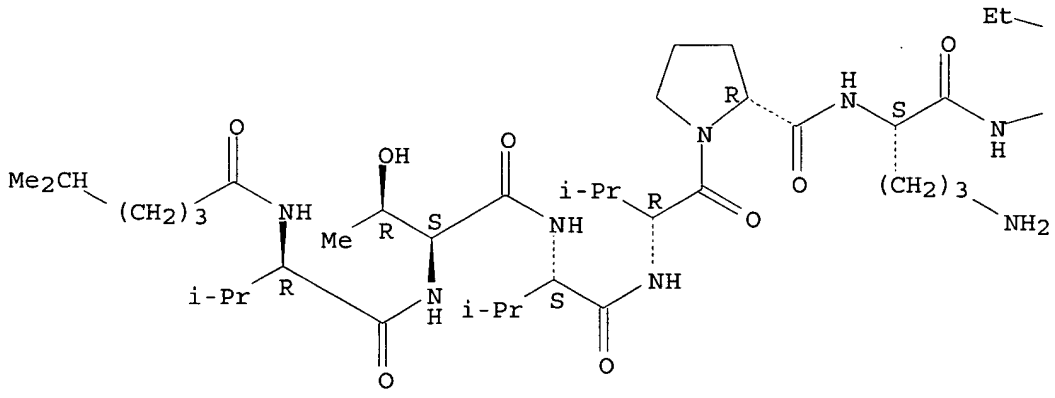
AB Kahalalide F(1) is a depsipeptide of 14 residues, five of which form a 19-membered ring. It was isolated from a marine mollusk, Elysia rufescens, and is currently in preclin. trails against lung and colon cancers. It was known from conventional amino acid anal. that five valine and two threonine residues represented D- and L-enantiomers, but their position in the mol. was not known. After extensive hydrolytic trials, a combination of acid hydrolysis and hydrazinolysis succeeded in definitive stereochem. assignment.

IT 149204-42-2, Kahalalide F
RL: PRP (Properties); RCT (Reactant); RACT (Reactant or reagent)
(absolute stereochem. of kahalalide F)

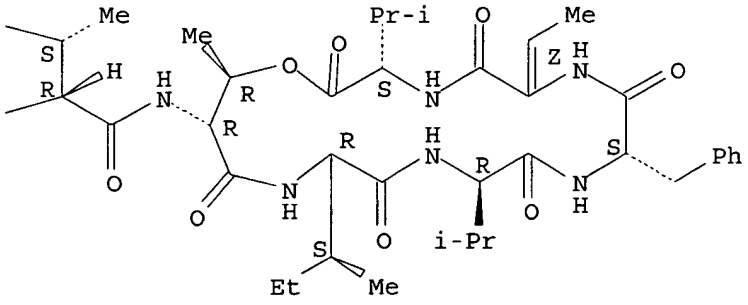
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 53 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:447351 HCAPLUS
DOCUMENT NUMBER: 129:228328
TITLE: Kahalalides: Bioactive Peptides from a Marine Mollusk Elysia rufescens and Its Algal Diet Bryopsis sp.. [Erratum to document cited in CA125:190997]
AUTHOR(S): Hamman, Mark T.; Otto, Clifton S.; Scheuer, Paul J.; Dunbar, D. Chuck
CORPORATE SOURCE: Department of Chemistry, University of Hawaii of Manoa, Honolulu, HI, 96822, USA
SOURCE: Journal of Organic Chemistry (1998), 63(14), 4856
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

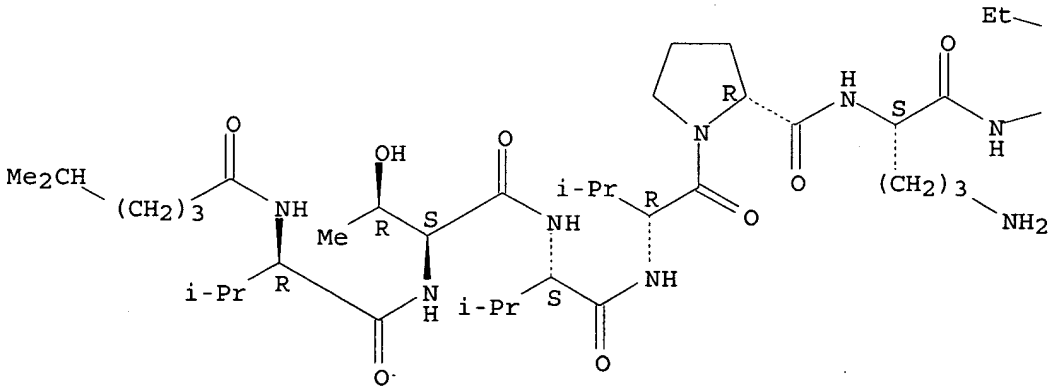
AB On page 6595, the labeled amino acid on the structure of kahalalide F (6) should read D-Pro rather than L-Pro.

IT 149204-42-2P, Kahalalide F
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(depsipeptide isolation and structural characterization and antitumor and antiviral activity from marine mollusk and green alga (Erratum))

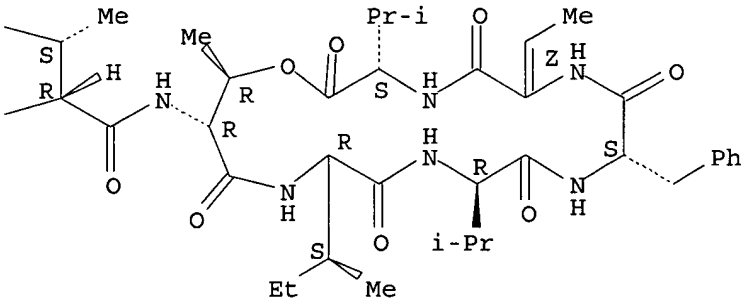
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



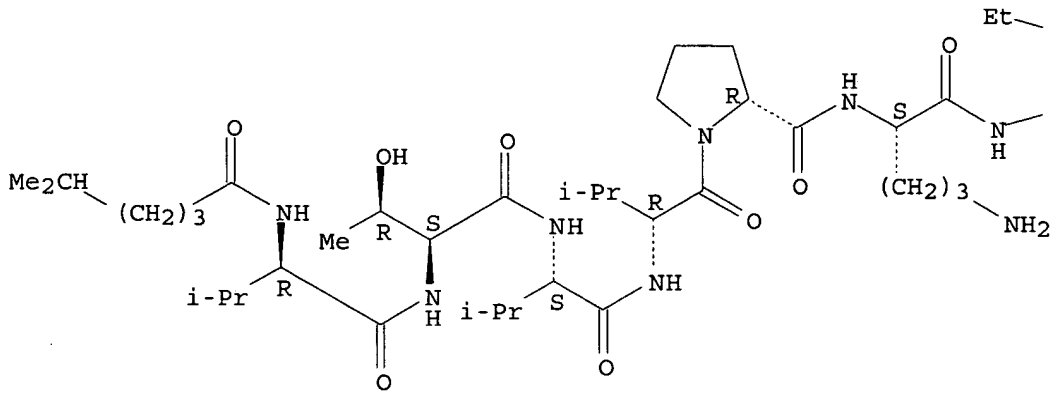
L12 ANSWER 54 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:403108 HCAPLUS
DOCUMENT NUMBER: 127:62001
TITLE: Marine natural products as prototype insecticidal agents
AUTHOR(S): El Sayed, Khalid A.; Dunbar, D. Charles; Perry, Tony L.; Wilkins, Scott P.; Hamann, Mark T.; Greenplate, John T.; Wideman, Margaret A.
CORPORATE SOURCE: Department of Pharmacognosy School of Pharmacy, University of Mississippi, University, MS, 38677, USA
SOURCE: Journal of Agricultural and Food Chemistry (1997), 45(7), 2735-2739
CODEN: JAFCAU; ISSN: 0021-8561
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an attempt to characterize addnl. structural classes that could serve as prototypes for insecticides, 26 structurally diverse marine compds. were examined for insecticidal activity in a diet overlay assay against newly hatched larvae of the southern corn rootworm, Diabrotica undecimpunctata howardi, and the tobacco budworm, Heliothis virescens. Several new classes of compds. have been identified as having potential as lead compds. for the development of new marine-derived insecticides.

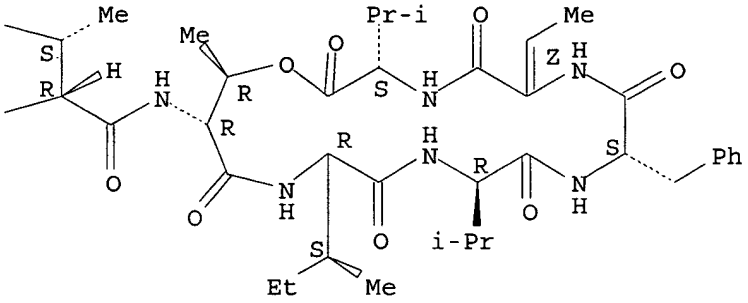
IT 149204-42-2, Kahalalide f
RL: AGR (Agricultural use); BIOL (Biological study); USES (Uses)
(marine natural products as insecticides)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 55 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:531764 HCAPLUS
DOCUMENT NUMBER: 125:190997
TITLE: Kahalalides: bioactive peptides from a marine mollusk Elysia rufescens and its algal diet Bryopsis sp.
AUTHOR(S): Hamann, Mark T.; Otto, Clifton S.; Scheuer, Paul J.; Dunbar, D. Chuck
CORPORATE SOURCE: Department of Chemistry, University of Hawaii of Manoa, Honolulu, HI, 96822, USA
SOURCE: Journal of Organic Chemistry (1996), 61(19), 6594-6600 CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In addition to the previously reported bioactive kahalalide F, 6 new peptides are described. Six of these, including kahalalide F, are cyclic depsipeptides, ranging from a C31 tripeptide to a C75 tridecapeptide isolated from a sacoglossan mollusk, E. rufescens. The mollusk feeds on a green alga, Bryopsis sp., which has also been shown to elaborate some of these peptides in smaller yields, in addition to an acyclic analog of F, kahalalide G. The bioassay results of antitumor, antiviral, antimalarial, and OI (activity against AIDS opportunistic infections) tests are

reported.

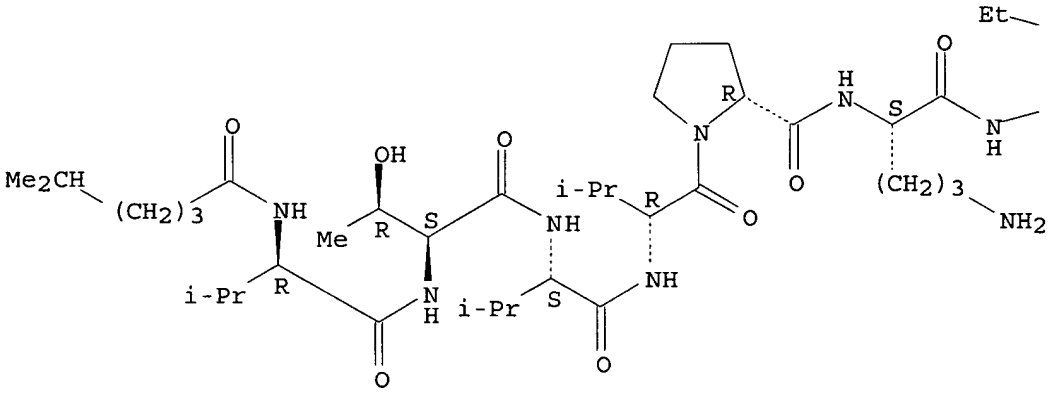
IT 149204-42-2P, Kahalalide F
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(depsipeptide isolation and structural characterization and antitumor and antiviral activity from marine mollusk and green alga)

RN 149204-42-2 HCAPLUS

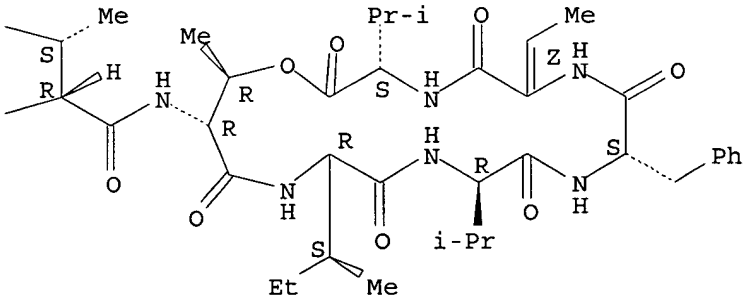
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 56 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:423809 HCAPLUS

DOCUMENT NUMBER: 125:131710

TITLE: The marine environment: A resource for prototype antimalarial agents

AUTHOR(S): El Sayed, Khalid A.; Dunbar, D. Charles; Goins, D. Keith; Cordova, Cindy R.; Perry, Tony L.; Wesson, Keena J.; Sanders, Sharon C.; Janus, Scott A.; Hamann, Mark T.

CORPORATE SOURCE: Center the Development Natural Products, University Mississippi, University, MS, 38677, USA

SOURCE: Journal of Natural Toxins (1996), 5(2), 261-285
CODEN: JNTOER; ISSN: 1058-8108
PUBLISHER: Alaken
DOCUMENT TYPE: Journal
LANGUAGE: English

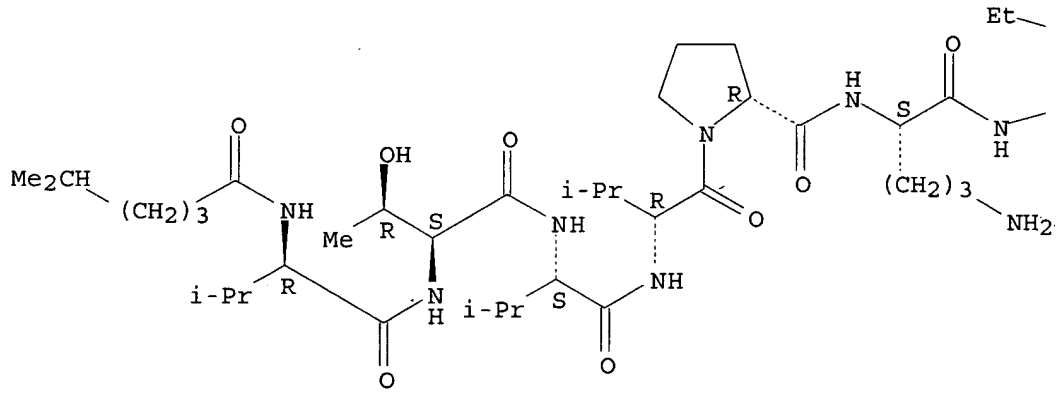
AB In an attempt to characterize addnl. structural classes that could serve as prototype antimalarial agents, 28 structurally diverse marine compds. were examined for in vitro activity against the D6 and W2 clones of Plasmodium falciparum. Several new classes of compds. have been identified as having potential as prototypes for the development of new antimalarial agents.

IT 149204-42-2, Kahalalide F
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(antimalarial activity of biomols. from marine organisms)

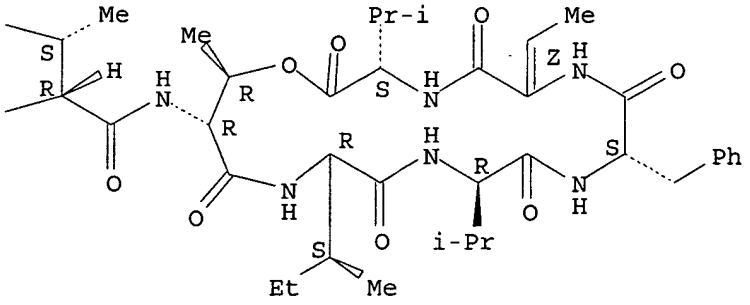
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L12 ANSWER 57 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:58580 HCAPLUS
DOCUMENT NUMBER: 124:164539

TITLE: The antitumoral compound Kahalalide F acts on cell lysosomes
AUTHOR(S): Garcia-Rocha, Mar; Bonay, Pedro; Avila, Jesus
CORPORATE SOURCE: 28049-Madrid, Spain
SOURCE: Cancer Letters (Shannon, Ireland) (1996), 99(1), 43-50
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

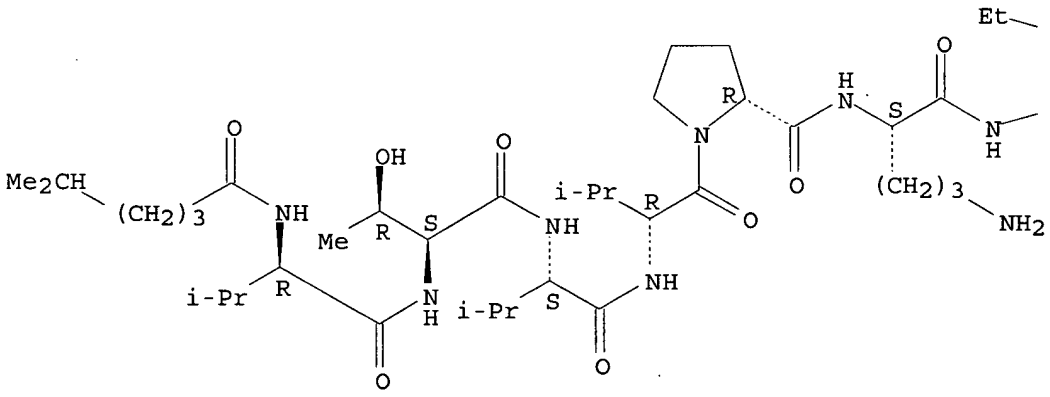
AB The target for the antitumoral peptidic drug, Kahalalide F, has been studied in cultured cells. In the presence of the compound, the cells became impressively swollen, showing the formation of large vacuoles. The formation of these vacuoles appears to be the consequence of changes in lysosomal membranes. Thus, lysosomes are a target for Kahalalide F action.

IT 149204-42-2, Kahalalide F
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(the antitumoral compound Kahalalide F acts on cell lysosomes)

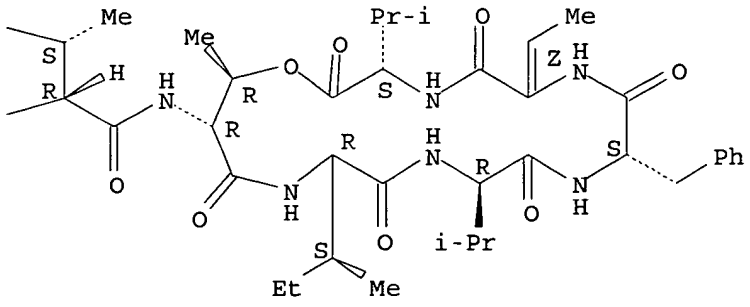
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



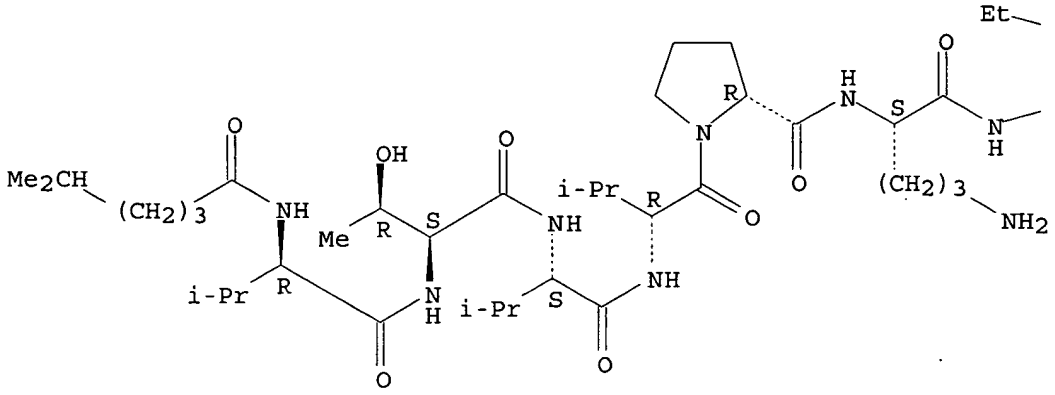
L12 ANSWER 58 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:130565 HCAPLUS
DOCUMENT NUMBER: 122:17167
TITLE: Kalahide F as cytotoxic and antiviral and antifungal compound
INVENTOR(S): Schauer, Paul J.; Hamann, Mark T.; Gravalos, Dolores G.
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 610078	A1	19940810	EP 1994-300780	19940202
EP 610078	B1	19970416		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 151776	E	19970515	AT 1994-300780	19940202
ES 2102772	T3	19970801	ES 1994-300780	19940202
CA 2114859	AA	19940804	CA 1994-2114859	19940203
AU 9454911	A1	19940811	AU 1994-54911	19940203
AU 677258	B2	19970417		
ZA 9400748	A	19940929	ZA 1994-748	19940203
JP 07070185	A2	19950314	JP 1994-43024	19940203
JP 3452628	B2	20030929		
PRIORITY APPLN. INFO.:			GB 1993-2046 A	19930203

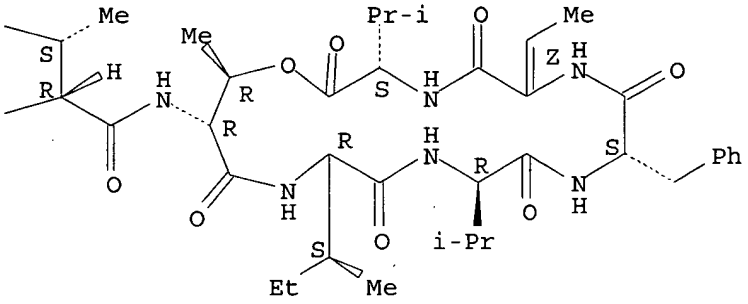
AB Kalahide F (I) which is isolated from sacoglossan may be used in the treatment of tumors or viral conditions. I was isolated from Elysia rufescens by extraction and silica gel flash chromatog. The antifungal, antiviral and cytotoxicity activity of I is shown.
IT 149204-42-2
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(kalahide F as cytotoxic and antiviral and antifungal compound)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



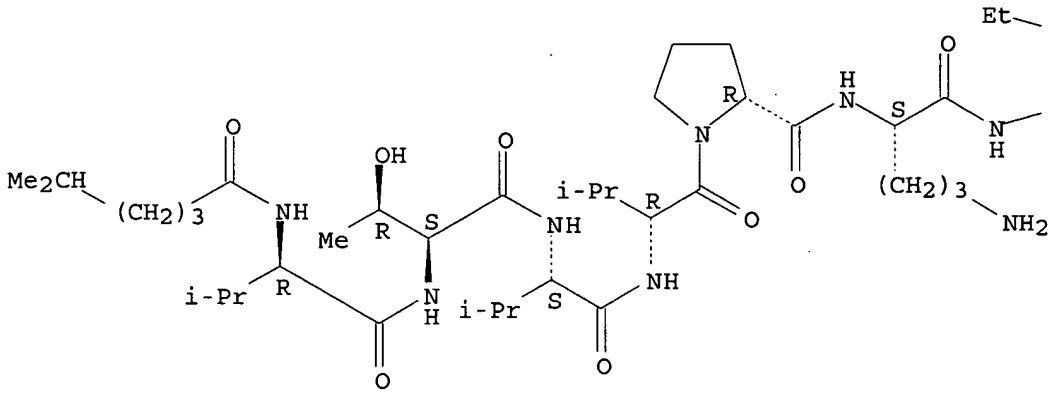
L12 ANSWER 59 OF 59 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:491602 HCAPLUS
DOCUMENT NUMBER: 119:91602
TITLE: Kahalalide F: a bioactive depsipeptide from the sacoglossan mollusk Elysia rufescens and the green alga Bryopsis sp
AUTHOR(S): Hamann, Mark T.; Scheuer, Paul J.
CORPORATE SOURCE: Dep. Chem., Univ. Hawaii, Honolulu, HI, 96822, USA
SOURCE: Journal of the American Chemical Society (1993), 115(13), 5825-6
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kahalalide F, C75H124N14O16, was isolated from a sacoglossan mollusk Elysia rufescens and its food source, a green alga, Bryopsis. Its structure was determined by spectral detns. and chiral amino acid anal.

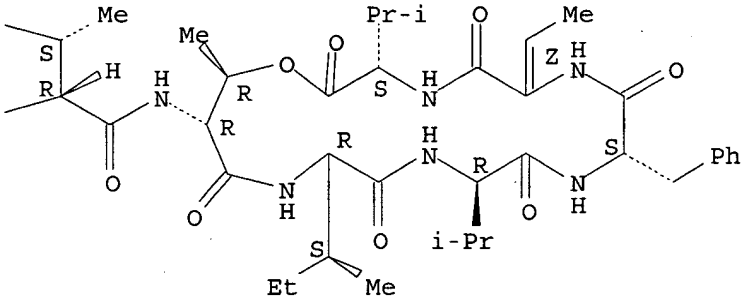
IT 149204-42-2, Kahalalide F
RL: BIOL (Biological study)
(of sacoglossan mollusk and green alga)
RN 149204-42-2 HCAPLUS
CN Kahalalide F (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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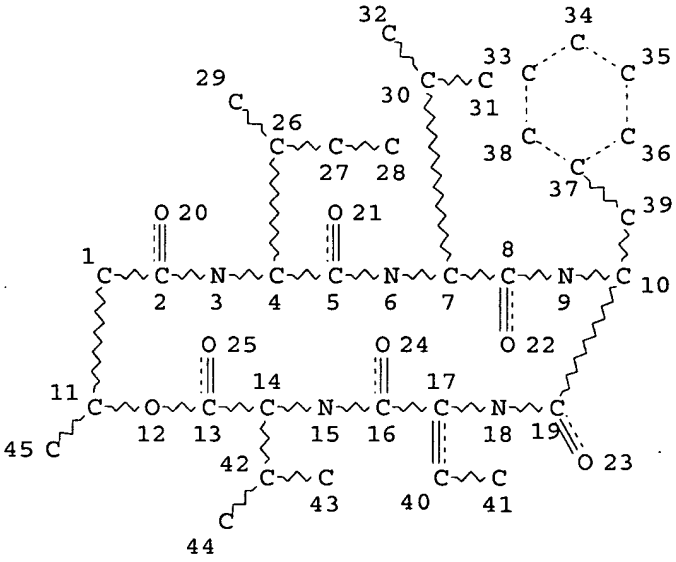

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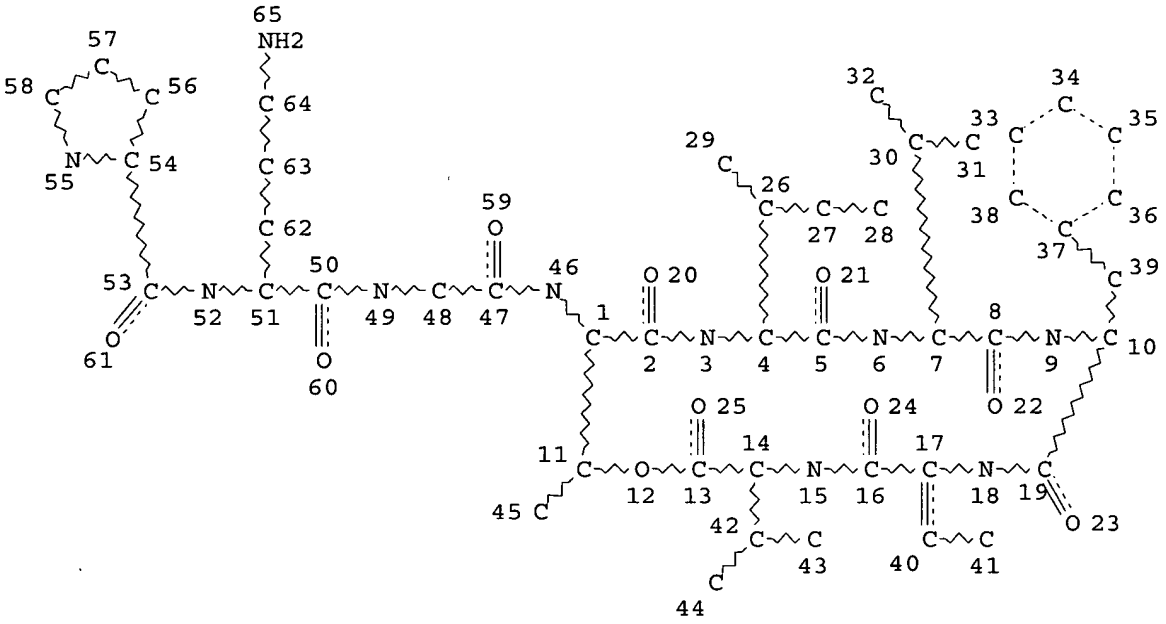
L5 156 SEA FILE=REGISTRY SSS FUL L3
L6 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 65

STEREO ATTRIBUTES: NONE
L7 125 SEA FILE=REGISTRY SUB=L5 SSS FUL L6
L12 59 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
L16 73 SEA FILE=HCAPLUS ABB=ON PLU=ON "FAIRCLOTH G"/AU OR "FAIRCLOTH G T"/AU OR ("FAIRCLOTH GLYNN"/AU OR "FAIRCLOTH GLYNN T"/AU OR "FAIRCLOTH GLYNN T JR"/AU OR "FAIRCLOTH GLYNN THOMAS"/AU)
L17 15 SEA FILE=HCAPLUS ABB=ON PLU=ON "CUEVAS M"/AU OR ("CUEVAS MARCHANTE CARMEN"/AU OR "CUEVAS MARCHANTE MARIA DEL CARMEN"/AU)

L18 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L16 AND L17
L19 65 SEA FILE=HCAPLUS ABB=ON PLU=ON (L16 OR L17) AND (?TUMOR? OR ?CANCER? OR ?NEOPLAS? OR ?MALIG?)
L20 58 SEA FILE=HCAPLUS ABB=ON PLU=ON (L18 OR L19) NOT L12

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=> d ibib abs hitstr l20 1-58

L20 ANSWER 1 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:868555 HCAPLUS
TITLE: Kahalalide F and ES285: potent anticancer agents from marine molluscs
AUTHOR(S): Faircloth, G.; Cuevas, C.
CORPORATE SOURCE: PharmaMar SA, Madrid, 28770, Spain
SOURCE: Progress in Molecular and Subcellular Biology (2006), 43(Molluscs), 363-379
CODEN: PMSBA4; ISSN: 0079-6484
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB The marine environment is proving to be a very rich source of unique compds. with significant activities against cancer of several types. Finding the sources of these new chemical entities has made it necessary for marine and medical scientists to find enterprising ways to collaborate in order to sample the great variety of intertidal, shallow and deep-water sea life. Recently these efforts resulted in a first generation of drugs from the sea undergoing clin. trials. These include PharmaMar compds.: Yondelis, Aplidin, kahalalide F, ES285 and Zalypsis. Two of these compds., kahalalide F and ES285, have been isolated from the Indopacific mollusc Elysia rufescens and the North Atlantic mollusc Spisula polynyma, resp.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:487280 HCAPLUS
TITLE: Induction of resistance to Aplidin in a human ovarian cancer cell line related to MDR expression
AUTHOR(S): Tognon, Gianluca; Bernasconi, Sergio; Celli, Nicola; Faircloth, Glynn T.; Cuevas, Carmen; Jimeno, Jose; Erba, Eugenio; D'Incalci, Maurizio
CORPORATE SOURCE: Department of Oncology, Flow Cytometry Unit, Mario Negri Institute, Milan, Italy
SOURCE: Cancer Biology & Therapy (2005), 4(12), 1325-1330
CODEN: CBTAAO; ISSN: 1538-4047
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aplidin-resistant IGROV-1/APL cells were derived from the human ovarian cancer IGROV-1 cell line by exposing the cells to increasing concentration of Aplidin for eight months, starting from a concentration of 10 nM to a final concentration of 4 μM. IGROV-1/APL cell line possesses five fold relative resistance to Aplidin. IGROV-1/APL resistant cell line shows the typical MDR phenotype: (1) increased expression of membrane-associated P-glycoprotein, (2) cross-resistance to drugs like etoposide, doxorubicin, vinblastine, vincristine, taxol, colchicine and the novel anticancer drug Yondelis (ET-743). The Pgp inhibitor cyclosporin-A restored the sensitivity of IGROV-1/APL cells to Aplidin by increasing the drug intracellular concentration The resistance to Aplidin was not due to the other proteins, such as LPR-1 and MRP-1, being expressed at the same level in resistant and parental cell line. The finding that cells over-expressing Pgp are resistant to Aplidin was confirmed in CEM/VLB 100 cells, that was found to be 5-fold resistant to Aplidin

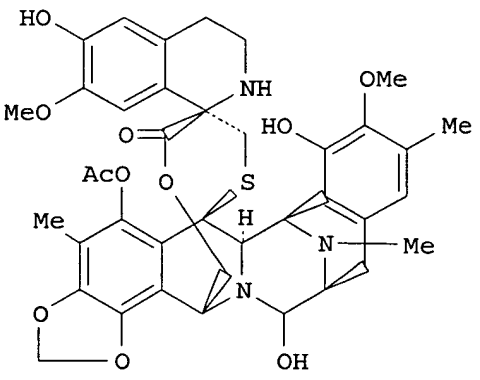
compared to the CEM parental cell line.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:319213 HCAPLUS
DOCUMENT NUMBER: 144:343581
TITLE: Ecteinascidin compounds as anti-inflammatory agents
INVENTOR(S): Allavena, Paola; D'Incalci, Maurizio; Faircloth, Glynn Thomas
PATENT ASSIGNEE(S): Pharma Mar S.A., Sociedad Unipersonal, Spain; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006035244	A2	20060406	WO 2005-GB50164	20050928
WO 2006035244	A3	20060831		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-614093P P 20040928
OTHER SOURCE(S): MARPAT 144:343581
GI



I

AB The anti-inflammatory activity of ecteinascidin compds. was determined Ecteinascidin 743 (I) and other ecteinascidin compds. affect viability and

functions of monocyte/macophages. Examples include noncytotoxic concs. of I inhibit in vitro and in vivo macrophage differentiation, I shows selective cytotoxic effect on mononuclear phagocytes, I inhibits the production of inflammatory cytokines/chemokines, and I was compared with antineoplastic agents currently used in ovarian cancer.

L20 ANSWER 4 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:203200 HCAPLUS
DOCUMENT NUMBER: 144:425023
TITLE: Quantitative analysis of Variolin analog (PM01218) in mouse and rat plasma by high-performance liquid chromatography/electrospray ionization tandem mass spectrometry
AUTHOR(S): Yin, Jianming; Aviles, Pablo; Ly, Carl; Lee, William; Guillen, Maria Jose; Munt, Simon; Cuevas, Carmen; Faircloth, Glynn
CORPORATE SOURCE: PharmaMar USA Inc., Cambridge, MA, 02139-4616, USA
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2006), 832(2), 268-273
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PM01218 is a novel marine-derived alkaloid and has shown potent growth inhibitory activity against several human cancer cell lines. A rapid and sensitive high performance liquid chromatog./tandem mass spectrometry (HPLC-MS/MS) method was developed and validated to quantify PM01218 in mouse and rat plasma. The lower limit of quantitation (LLOQ) was 0.05 ng/mL. The calibration curve was linear from 0.05 to 100 ng/mL (R2 > 0.999). The assay was specifically based on the multiple reaction monitoring (MRM) transitions at m/z 278.4→184.2, no endogenous material interfaced with the anal. of PM01218 and its internal standard from blank mouse and rat plasma. The mean intra- and inter-day assay accuracy remained below 15 and 8%, resp., for all calibration stds. and QC samples. The intra- and inter-day assay precision was less than 12.8 and 8.5% for all QC levels, resp. The utility of the assay was demonstrated by pharmacokinetics studies of i.v. (bolus) PM01218 on SD rats.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:730756 HCAPLUS
DOCUMENT NUMBER: 143:278611
TITLE: Combination of trabectedin and irinotecan is highly effective in a human rhabdomyosarcoma xenograft
AUTHOR(S): Riccardi, Anna; Meco, Daniela; Ubezio, Paolo; Mazzarella, Giorgio; Marabese, Mirko; Faircloth, Glynn T.; Jimeno, Jose; D'Incalci, Maurizio; Riccardi, Riccardo
CORPORATE SOURCE: Department of Pediatric Oncology, Catholic University, Rome, Italy
SOURCE: Anti-Cancer Drugs (2005), 16(8), 811-815
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our objective was to evaluate in vitro and in vivo the effect of the combination of trabectedin (Yondelis, ET-743) and irinotecan (CPT-11) or its major metabolite SN-38 in a human rhabdomyosarcoma cell line. The

schedule trabectedin (1 h) followed by irinotecan or SN-38 (24 h) and the opposite sequence (irinotecan or SN-38 24 h followed by trabectedin 1 h) were analyzed in a rhabdomyosarcoma cell line. In vivo studies were conducted with trabectedin and irinotecan at the doses of 0.2 and 20 mg/kg, resp., simultaneously administered with a q4d + 3 schedule. In vitro studies indicated an overall additive effect [combination index (CI) relatively close to 1.0], with the former schedule slightly superior to the latter (at the IC50 effect levels: CI = 0.89 vs. 1.07). Neither transcription nor expression of DNA topoisomerase I was affected by trabectedin treatment. In vivo the therapeutic results of the combination were certainly more impressive: trabectedin and irinotecan combination caused a strong and long-lasting effect on tumor growth (tumor volume inhibition = 89%, log10 cell kill = 1.6), whereas each drug given as a single agent was only marginally active. The discrepancy between the in vitro and in vivo results suggests possible mechanisms involving host cells, other than tumor cells. The striking effects of the combination observed in vivo could be related to a combination of a direct cytotoxic and an anti-inflammatory indirect effect. The very marked and long-lasting effect of the trabectedin and irinotecan combination in vivo suggests a basis for a clin. evaluation in pediatric patients with rhabdomyosarcoma.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:218200 HCAPLUS
DOCUMENT NUMBER: 142:430441
TITLE: Development of a liquid chromatography/tandem mass spectrometry assay for the quantification of PM00104, a novel antineoplastic agent, in mouse, rat, dog, and human plasma
AUTHOR(S): Yin, Jianming; Aviles, Pablo; Lee, William; Ly, Carl; Guillen, Maria Jose; Munt, Simon; Cuevas, Carmen; Faircloth, Glynn
CORPORATE SOURCE: PharmaMar USA, Inc., Cambridge, MA, 02139-4616, USA
SOURCE: Rapid Communications in Mass Spectrometry (2005), 19(5), 689-695
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A rapid and sensitive liquid chromatog./tandem mass spectrometry (LC/MS/MS) assay was developed and validated to quantify a novel antineoplastic agent, PM00104, in mouse, rat, dog, and human plasma. The method was validated to demonstrate the specificity, limit of quantification (LOQ), accuracy, and precision of measurements. The calibration range for PM00104 was established using PM00104 stds. from 0.01-5.0 ng/mL in blank plasma. The selected reaction monitoring (SRM), based on the m/z 692.2 → 218.2 transition, was specific for PM00104, and that based on the m/z 697.2 → 218.2 transition was specific for PM00104 (13C2,2H3) (the internal standard, IS); no endogenous materials interfered with the anal. of PM00104 and IS from blank plasma. The assay was linear over the concentration range 0.01-5.0 ng/mL. The correlation coeffs. for the calibration curves ranged from 0.9981-0.9999. The mean intra-day and inter-day accuracies for all calibration stds. (n = 8) ranged from 97-105% (≤5% bias) in human plasma, and the mean inter-day precision for all calibration stds. was less than 8.5%. The mean intra- and inter-day assay accuracy for all quality control (QC) replicates in human plasma (n = 9), determined at each QC level throughout the validated runs, ranged from 96-112% (≤12% bias) and from 102-105%

(≤5% bias), resp. The mean intra- and inter-day assay precision was less than 15.0 and 11.8% for all QC levels, resp. For the QC samples prepared in animal species plasma, the %CV values of the assays ranged from 1.8-8.8% in mouse plasma, from 3.7-13.8% in rat plasma, and from 3.0-7.2% in dog plasma. The assay accuracies ranged from 92-102% (≤8% bias) for all QC levels prepared in mouse plasma; ranged from 93-106% (≤7% bias) in rat plasma; and ranged from 95-114% (≤14% bias) in dog plasma. The assay was used to support preclin. pharmacokinetic and toxicokinetic studies and is currently used to measure PM00104 plasma concns. to support clin. trials.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:128729 HCAPLUS
DOCUMENT NUMBER: 142:348389
TITLE: The unique biological features of the marine product Yondelis (ET-743, trabectedin) are shared by its analog ET-637, which lacks the C ring
AUTHOR(S): Erba, E.; Cavallaro, E.; Damia, G.; Mantovani, R.; Di Silvio, A.; Di Francesco, A. M.; Riccardi, R.; Cuevas, C.; Faircloth, G. T.; D'Incalci, M.
CORPORATE SOURCE: Department of Oncology, Mario Negri Institute for Pharmacological Research, Milan, 20157, Italy
SOURCE: Oncology Research (2004), 14(11/12), 579-587
CODEN: ONREE8; ISSN: 0965-0407
PUBLISHER: Cognizant Communication Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It was previously suggested that the peculiar mechanism of action of the novel anticancer drug Yondelis (ET-743, trabectedin) was due to part of the mol., units A and B, binding to DNA in the minor groove, causing an alkylation at the N2 of guanine, while unit C protrudes out of DNA, possibly interacting with transcription factors or other DNA binding proteins. To test this hypothesis, we have compared the biol. activity and the mode of action of Yondelis with its analog ET-637, which has the same chemical structure except for the lack of the C ring. Yondelis and ET-637 showed similar cytotoxic potency and cell cycle perturbations. As already reported for Yondelis, the UV-96 cell line, deficient in ERCC-1, was less sensitive to ET-637 than the parental cell line. The binding of Yondelis or ET-637 to DNA-oligonucleotides was demonstrated by gel shift assay and SDS did not reverse the binding. Both compds. blocked the temperature-induced activation of the HSP40 promoter in the range of 1-10 nM. This study indicates that ET-637 acts similarly to Yondelis and demonstrates that the C ring of Yondelis may not be required for its biol. activity.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:69115 HCAPLUS
DOCUMENT NUMBER: 143:278434
TITLE: Molecular characterisation of two human cancer cell lines selected in vitro for their chemotherapeutic drug resistance to ET-743
AUTHOR(S): Marchini, S.; Marrazzo, E.; Bonomi, R.; Chiorino, G.; Zaffaroni, M.; Weissbach, L.; Hornicek, F. J.; Broggini, M.; Faircloth, G. T.; D'Incalci, M.
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Department of

Oncology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy
SOURCE: European Journal of Cancer (2005), 41(2), 323-333
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB ET-743 (Yondelis, Trabectedin) isolated from the tunicate Ecteinascidia turbinata, is being tested in phase II clin. trials in Europe and the United States of America (USA). Studies with different solid tumors have shown antitumor activity in advanced, pre-treated sarcomas as well as in drug-resistant breast and ovarian cancer. The primary mechanism of action for ET-743 has not been fully elucidated and different models have been suggested to explain its mol. mechanism of action. ET-743 binds tightly to the minor groove of DNA and previous data have suggested that ET-743 acts by interfering with RNA transcription. To further investigate the mechanism of in vitro drug resistance, we evaluated the gene expression profile in ovarian and chondrosarcoma cell lines selected for resistance to ET-743. We found 70 genes whose expression was modulated in both drug-resistant cell lines when compared with their resp. parental drug-sensitive cell lines. This pattern of gene expression seems to be selective for ET-743-resistant cells, since ovarian cancer cells resistant to paclitaxel did not share the same gene expression changes. Data presented in this study reveal different mol. pathways that could be involved in the cellular mechanism of ET-743 resistance.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:817412 HCAPLUS
DOCUMENT NUMBER: 141:307511
TITLE: Antitumor spisulosine compounds
INVENTOR(S): Rinehart, Kenneth L.; Warwick, Robert A.; Avila, Jesus; Fregeau Gallagher, Nancy L.; Garcia Gravalos, Dolores; Faircloth, Glynn T.
PATENT ASSIGNEE(S): Board of Trustees of the University of Illinois, USA
SOURCE: U.S., 23 pp., Cont.-in-part of U.S. 6,107,520.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6800661	B1	20041005	US 1999-386724	19990831
US 6107520	A	20000822	US 1998-58456	19980410
US 38793	E	20050906	US 2002-219050	20020814
US 2004147615	A1	20040729	US 2003-693174	20031023
US 2006183806	A9	20060817		
US 7109244	B2	20060919		

PRIORITY APPLN. INFO.:

US 1997-43326P	P	19970415
US 1997-43599P	P	19970415
US 1998-58456	A2	19980410
US 1999-386724	A1	19990831

AB Investigation of the activity of exts. of the clam Spisula polynyma has led to antitumor long-chain, straight-chain alkane or alkene compds. which have a 2-amino group and a 3-hydroxy group. Isolation and preparation of spisulosine compds. are described.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:780551 HCAPLUS
DOCUMENT NUMBER: 141:254554
TITLE: Aplidine for multiple myeloma treatment
INVENTOR(S): Bertino, Joseph R.; Medina, Daniel; Faircloth, Glynn Thomas; Mitsiades, Constantine S.
PATENT ASSIGNEE(S): Dana-Faber Cancer Institute, Inc., USA; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004080477	A1	20040923	WO 2004-GB1062		20040312
WO 2004080477	C1	20041111			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2004218883	A1	20040923	AU 2004-218883		20040312
CA 2519789	AA	20040923	CA 2004-2519789		20040312
EP 1603584	A1	20051214	EP 2004-720081		20040312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK					
CN 1761480	A	20060419	CN 2004-80006724		20040312
JP 2006519828	T2	20060831	JP 2006-505957		20040312
NO 2005004668	A	20051011	NO 2005-4668		20051011
US 2006172926	A1	20060803	US 2006-548710		20060411
PRIORITY APPLN. INFO.:			US 2003-454125P	P	20030312
			US 2003-520293P	P	20031114
			WO 2004-GB1062	W	20040312

AB Aplidine and aplidine analogs are used in the manufacture of a medicament for treating multiple myeloma.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:780508 HCAPLUS
DOCUMENT NUMBER: 141:271548
TITLE: Improved antitumor treatments using aplidine and aplidine analogs in combination with other drugs
INVENTOR(S): Barnejee, Debabrata; Bertino, Joseph R.; Faircloth, Glynn Thomas; Guray, Saydam; Jimeno, Jose
PATENT ASSIGNEE(S): Pharma Mar S.A., Spain
SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004080421	A2	20040923	WO 2004-US7606	20040312
WO 2004080421	A3	20050609		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004220451	A1	20040923	AU 2004-220451	20040312
CA 2516572	AA	20040923	CA 2004-2516572	20040312
EP 1620117	A2	20060201	EP 2004-720399	20040312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1753684	A	20060329	CN 2004-80005179	20040312
JP 2006519848	T2	20060831	JP 2006-507125	20040312
NO 2005003947	A	20051207	NO 2005-3947	20050824
US 2006178298	A1	20060810	US 2005-546750	20051104
PRIORITY APPLN. INFO.:			US 2003-454125P P	20030312
			WO 2004-US7606 W	20040312

AB Aplidine and aplidine analogs are of use for the treatment of cancer, in particular in the treatment of leukemias and lymphomas, especially in combination therapies.

L20 ANSWER 12 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:462251 HCAPLUS
DOCUMENT NUMBER: 142:32543
TITLE: Antiangiogenic activity of aplidine, a new agent of marine origin
AUTHOR(S): Taraboletti, G.; Poli, M.; Dossi, R.; Manenti, L.; Borsotti, P.; Faircloth, G. T.; Broggini, M.; D'Incalci, M.; Ribatti, D.; Giavazzi, R.
CORPORATE SOURCE: Department of Oncology, Mario Negri Institute, Bergamo, 24125, Italy
SOURCE: British Journal of Cancer (2004), 90(12), 2418-2424
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antineoplastic compound aplidine, a new marine-derived depsipeptide, has shown preclin. activity in vitro on hematol. and solid tumor cell lines. It is currently in early phase clin. trials. The exact mechanism of action of this anticancer agent still needs to be clarified. We have previously reported that aplidine blocks the secretion of the angiogenic factor vascular endothelial growth factor (VEGF) by the human leukemia cells MOLT-4, suggesting a possible effect on tumor angiogenesis. This study was designed to investigate the antiangiogenic effect of aplidine. In vivo, in the chick embryo allantoic

membrane (CAM) assay, aplidine inhibited spontaneous angiogenesis, angiogenesis elicited by exogenous VEGF and FGF-2, and induced by VEGF over-expressing 1A9 ovarian carcinoma cells. In vitro, at concns. achievable in the plasma of patients, aplidine inhibited endothelial cell functions related to angiogenesis. It affected VEGF- and FGF-2-induced endothelial cell proliferation, inhibited cell migration and invasiveness assessed in the Boyden chamber and blocked the production of matrix metalloproteinases (MMP-2 and MMP-9) by endothelial cells. Finally, aplidine prevented the formation of capillary-like structures by endothelial cells on Matrigel. These findings indicate that aplidine has antiangiogenic activity in vivo and inhibits endothelial cell functional responses to angiogenic stimuli in vitro. This effect might contribute to the antineoplastic activity of aplidine.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:267824 HCAPLUS
DOCUMENT NUMBER: 141:270761
TITLE: New marine derived anticancer therapeutics - a journey from the sea to clinical trials
AUTHOR(S): Jimeno, J.; Faircloth, G.; Fernandez Souse-Faro, J. M.; Scheuer, P.; Rinehart, K.
CORPORATE SOURCE: PharmaMar R & D, Madrid, Spain
SOURCE: Marine Drugs (2004), 2(1), 14-29
CODEN: MDARE6; ISSN: 1660-3397
URL: http://www.mdpi.net/marinedrugs/papers/papers03/md101005.pdf
PUBLISHER: MDPI Center
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. Nature has been instrumental as a source for therapeutics. Despite the fact that we live in an oceanic planet, a number of tech. factors have historically hampered the evolution of a marine-based chamanic medicine. With the implementation of scuba diving tools and the development of sophisticated instruments for the isolation and elucidation of structures of natural products from marine organisms, major advances have been made in the discovery of marine derived therapeutics. The availability of ARA-C, a nucleoside analog that is a basic component in the treatment of acute myeloid leukemia, and its fluorinated analog Gemcitabine, an important therapeutic tool in the treatment of pancreatic cancer and in non small cell lung cancer, is a solid proof and validation of the potential of this approach. As a result of our discovery and developmental program, three innovative compds. with novel mechanisms of action: ET-743, Aplidin and Kahalalide F, have been shown to display a pos. therapeutic index and activity in resistant solid tumors that supports the ongoing clin. phase III/II trials. ET-743 represents the first active agent against sarcomas developed in the past 25 yr and has demonstrated a therapeutic potential in pretreated ovarian cancer. Several chemical entities are under advanced preclin. testing and addnl. candidates for clin. development are emerging, including compds. hitting a specific target. Moreover, the development of a given marine candidate implies the collaboration of an interdisciplinary team special focused on supply, formulation, pharmacogenetics and preclin. toxicol.

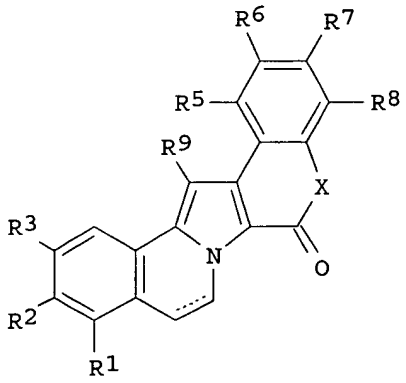
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 14 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:143159 HCAPLUS

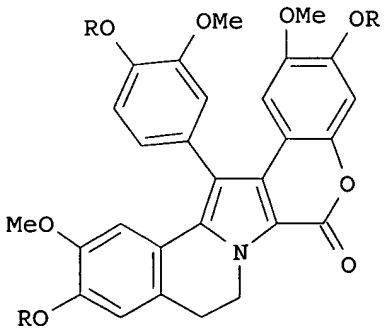
DOCUMENT NUMBER: 140:199492
TITLE: Preparation and antitumor activity of analogs of lamellarins
INVENTOR(S): Bailly, Christian; Francesch Solloso, Andres; Mateo Urbano, Maria Cristina; Jimenez Guerrero, Jose Antonio; Pastor Del Castillo, Alfredo; Cuevas Marchante, Carmen
PATENT ASSIGNEE(S): Pharma Mar, S.A.U., Spain; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014917	A2	20040219	WO 2003-GB3541	20030813
WO 2004014917	A3	20040513		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2493725	AA	20040219	CA 2003-2493725	20030813
AU 2003252997	A1	20040225	AU 2003-252997	20030813
EP 1551844	A2	20050713	EP 2003-784300	20030813
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1688585	A	20051026	CN 2003-824160	20030813
JP 2005536529	T2	20051202	JP 2004-527072	20030813
NO 2005001282	A	20050511	NO 2005-1282	20050310
US 2006173030	A1	20060803	US 2005-524151	20050801
PRIORITY APPLN. INFO.:			GB 2002-18816 A	20020813
			WO 2003-GB3541 W	20030813

OTHER SOURCE(S): MARPAT 140:199492
GI



I



II

AB The present invention discloses preparation of lamellarin analogs, such as I [X = N, O, S; R1, R2, R3, R4, R5, R6, R7, R8, R9 = H, OH, OR, SH, SR, SO2R, NHR, N(R)2, N:R, NHCOR, N(COR)2, NHSO2R, NO2, PO(R)2, PO2R, C(:O)H, C(:O)R, CO2H, CO2R, OPO(R)2, OPO2(R)2, OC(:O)H, OC(:O)R, N:C(R)2, un(substituted) C1-C12 alkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroarom.; R = H, OH, NO2, NH2, SH, CN, halo, :O, C(:O)H, COCH3, CO2H, (un)substituted C1-C18 alkyl, alkenyl, alkynyl, aryl, alkoxyl, aminoalkyl, amino acid, thioalkyl, alkylsulfinyl, alkylsulfonyl; R1R2, R2R3, R3R4, R3R9, R4R9, R9R5, R9R6, R6R7, R7R8 = carbocyclic or heterocyclic ring; dotted bond = single bond or double bond], or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof. Thus, lamellarin derivative II (R = COCH2CH2C6H5) was prepared via a multistep reaction sequence starting from 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline, iodo-acetic acid 5-isopropoxy-2-(4-isopropoxy-3-methoxyphenyl-ethynyl)-4-methoxyphenyl ester and hydrocinnamoyl chloride. The prepared lamellarin analogs were tested for antitumor activity against erythroleukemia, lung carcinoma, malignant melanoma, colon adenocarcinoma, prostate carcinoma, breast adenocarcinoma, ovary adenocarcinoma, cervix epithelioid carcinoma and pancreatic epitheloid carcinoma.

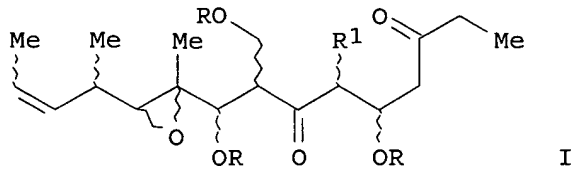
L20 ANSWER 15 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:101159 HCAPLUS
DOCUMENT NUMBER: 140:145931
TITLE: Total synthesis of myriaporones as antitumor agents
INVENTOR(S): Perez Alvarez, Marta; Del Pozo Losada, Carlos; Francesch Solloso, Andres; Cuevas Marchante, Carmen
PATENT ASSIGNEE(S): Pharma Mar, S.A.U., Spain; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004011458	A1	20040205	WO 2003-GB3327	20030730
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2494532	AA	20040205	CA 2003-2494532	20030730
AU 2003248984	A1	20040216	AU 2003-248984	20030730
EP 1532139	A1	20050525	EP 2003-771210	20030730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1684956	A	20051019	CN 2003-823314	20030730
JP 2006504659	T2	20060209	JP 2004-523987	20030730
NO 2005001037	A	20050413	NO 2005-1037	20050225
US 2006084819	A1	20060420	US 2005-523172	20050901

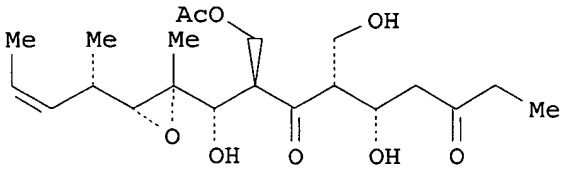
PRIORITY APPLN. INFO.: GB 2002-17638 A 20020730
WO 2003-GB3327 W 20030730

OTHER SOURCE(S): MARPAT 140:145931

GI



I



II

AB Myriaporones of formula I [R = H, trialkylsilyl, acyl, etc.; R1 = H, (substituted) OH, acyloxy, SH, CHO, CO2H, CH2OH, NH2, etc.] are prepared as antitumor agents. Thus, II was prepared in several steps. and shown to have activity against a number of tumor cell lines.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 16 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:980288 HCAPLUS
DOCUMENT NUMBER: 141:153093
TITLE: In vitro interaction between Ecteinascidin 743 (ET-743) and radiation, in relation to its cell cycle effects
AUTHOR(S): Simoens, C.; Korst, A. E. C.; De Pooter, C. M. J.; Lambrechts, H. A. J.; Pattyn, G. G. O.; Faircloth, G. T.; Lardon, F.; Vermorken, J. B.
CORPORATE SOURCE: Department of Medical Oncology, Laboratory of Cancer Research and Clinical Oncology, University of Antwerp (UIA/UZA), Antwerp, B-2610, Belg.
SOURCE: British Journal of Cancer (2003), 89(12), 2305-2311
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ecteinascidin 743 (ET-743) is a new marine-derived agent with promising activity against a number of solid tumors. In four human tumor cell lines, the interaction between ET-743 and radiation was investigated in relation to the effects of ET-743 on the cell cycle, in vitro. Cell survival was measured based on quant. staining of cellular protein by sulforhodamine B. A 24 h treatment with ET-743 before radiation resulted in a moderate increase in radiosensitivity in three out of four cell lines. Dose enhancement factors ≥1.8 were observed for concns. resulting in 52, 46 and 30% cell kill in ECV304, H292 and CAL-27, resp., whereas in A549 no radiosensitization was observed (no significant increase in radiosensitivity). According to the combination index anal., synergism was observed only in ECV304 and CAL-27 cells. A 24 h incubation with ET-743 resulted in a concentration-dependent G2/M block, which might explain the moderate radiosensitizing effects in ECV304 and H292. The lack of

radiosensitization in A549 might be due to the S phase delay preceding the G2/M block at the moment of radiation, which only occurred in this cell line. In conclusion, ET-743 has moderate cell line-dependent radiosensitizing properties; however, only when cytotoxic concns. of ET-743 are used. In one of the four cell lines tested, no radiosensitization was observed

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 17 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:869631 HCAPLUS
DOCUMENT NUMBER: 140:210099
TITLE: Use of CFU-GM assay for prediction of human maximum tolerated dose of a new antitumoral drug: Yondelis (ET-743)
AUTHOR(S): Gomez, Susana G.; Bueren, Juan A.; Faircloth, Glynn; Albella, Beatriz
CORPORATE SOURCE: S.A. Poligono Industrial La Mina, PharmaMar, Madrid, 28770, Spain
SOURCE: Toxicology in Vitro (2003), 17(5/6), 671-674
CODEN: TIVIEQ; ISSN: 0887-2333
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute cytotoxic exposure causes decreases in bone marrow progenitors that precedes the neutrophil nadir. Expts. in animal models reveal a relationship between the reduction in granulocyte-macrophage progenitors (CFU-GM) and the decrease in absolute neutrophil count [Toxicol. Pathol. 21 (1993) 241]. Recently, the prevalidation of a model for predicting acute neutropenia by the CFU-GM assay has been reported [Toxicol. In Vitro 15 (2001) 729]. The model was based on prediction of human MTD by adjusting the animal-derived MTD for the differential sensitivity between CFU-GM from animal species and humans. In this study, this model has been applied on a new antitumoral drug, Yondelis (Ecteinascidin; ET-743). Preclin. studies showed that hematotoxicity was the main side effect in mice, being the MTD of 600 μg/m2 [Drugs Future 21 (1996) 1155]. The sensitivity of myeloid progenitors was higher in mice than in humans, with IC90 values of 0.69±0.22 nM and 1.31±0.21 nM for murine and human CFU-GMs resp. This study predicts a human MTD of 1145 μg/m2. The reported human MTD of ET-743 given as a 24-h continuous infusion every 3 wk is 1800 μg/m2 [J. Clin. Oncol. 19 (2001) 1256]. Since our predicted MTD is within fourfold of the actual MTD (the interspecies variation in tolerated dose due to differences in clearance rates, metabolism pathways and infusion rate) the result confirms the profit of the prediction model.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 18 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:645662 HCAPLUS
DOCUMENT NUMBER: 140:174543
TITLE: The combination of yondelis and cisplatin is synergistic against human tumor xenografts
AUTHOR(S): D'Incalci, M.; Colombo, T.; Ubezio, P.; Nicoletti, I.; Giavazzi, R.; Erba, E.; Ferrarese, L.; Meco, D.; Riccardi, R.; Sessa, C.; Cavallini, E.; Jimeno, J.; Faircloth, G. T.
CORPORATE SOURCE: Department of Oncology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy
SOURCE: European Journal of Cancer (2003), 39(13), 1920-1926

CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB YondelisTM (trabectidin, ET-743) is a marine natural product that has shown activity both in preclin. systems and in human malignancies such as soft tissue sarcoma and ovarian cancers that are resistant to previous chemotherapies. Mol. pharmacol. studies indicated that Yondelis interacts with DNA and DNA repair systems in a way that is different from cisplatin (DDP). The current study was designed to investigate the effects of the combination of Yondelis and DDP in human cancer cell lines and in xenografts derived from different tumors. The in vitro studies performed in human TE-671 rhabdomyosarcoma, Igrov-1 and 1A9 human ovarian carcinoma cell lines showed additive effects or slight synergism. Several human tumor xenografts, such as TE-671 rhabdomyosarcoma, SK-N-DX neuroblastoma, FADU head and neck, LX-1 non-small cell lung cancer (NSCLC), H-187 melanoma and SKOV HOC 8 ovarian carcinoma, showed an antitumor effect for the combination that was greater than that of each drug when given as a single agent. No consistent changes in the activity were observed if Yondelis and DDP were given 1 h apart in sequence or simultaneously. An orthotopically transplanted human ovarian cancer HOC 8 growing in the peritoneal cavity of nude mice was used that is insensitive to Yondelis alone and only moderately sensitive to DDP alone. The combination of the two drugs produced a dramatic increase of survival lasting several months. In conclusion, the combination of Yondelis and DDP is synergistic in vivo (i.e. the antitumor effect is greater than that of each drug used as a single agent at the maximum tolerated dose (MTD)) in different human tumor xenografts. The two drugs can be combined at the MTD of each drug, thus indicating there are no overlapping toxicities. These results provide a rationale for testing the combination of Yondelis and DDP in the clinic.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 19 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:638934 HCAPLUS
DOCUMENT NUMBER: 140:283822
TITLE: Development of a liquid chromatography/tandem mass spectrometry assay for the quantification of Aplidin, a novel marine-derived antineoplastic agent, in human plasma
AUTHOR(S): Yin, Jianming; Aviles, Pablo; Lee, William; Ly, Carl; Floriano, Pablo; Ignacio, Manzanares; Faircloth, Glynn
CORPORATE SOURCE: PharmaMar USA, Inc., Cambridge, MA, 02139-4616, USA
SOURCE: Rapid Communications in Mass Spectrometry (2003), 17(16), 1909-1914
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid and sensitive liquid chromatog./tandem mass spectrometry (LC/MS/MS) assay was developed and validated to quantify a novel marine-derived depsipeptide, Aplidin, in human plasma. The method was validated to demonstrate the specificity, recovery, limit of quantitation (LOQ), accuracy, and precision of measurements. The calibration range for Aplidin was established using Aplidin stds. from 0.05-50 ng/mL in blank human plasma. The multiple reaction monitoring, based on the transition m/z 1110.7→295.3, was specific for Aplidin, and that based on the

transition m/z 1112.6→297.3 was specific for didemnin B (the internal standard); no endogenous materials interfered with the anal. of Aplidin and didemnin B from blank human plasma. The assay was linear over the concentration range 0.05-50.0 ng/mL. The correlation coeffs. for the calibration curves ranged from 0.9979 to 0.9999. The mean intra- and interday accuracies for all calibration stds. (n = 12) ranged from 97 to 106% (≤6% bias), and the mean interday precision for all calibration stds. was less than 8.3%. The mean intra- and interday assay accuracy for all quality control replicates (n = 12), determined at each QC level throughout the validated runs, remained below 12 and 7%, resp. The mean intra- and interday assay precision was less than 13.1 and 10.7% for all QC levels, resp. The assay is currently used to measure Aplidin plasma concns. to support clin. trials.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 20 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:616930 HCAPLUS
DOCUMENT NUMBER: 140:156856
TITLE: Effect of aplidine in acute lymphoblastic leukaemia cells
AUTHOR(S): Erba, E.; Serafini, M.; Gaipa, G.; Tognon, G.; Marchini, S.; Celli, N.; Rotilio, D.; Broggini, M.; Jimeno, J.; Faircloth, G. T.; Biondi, A.; D'Incalci, M.
CORPORATE SOURCE: Department of Oncology, Flow Cytometry Unit, Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, 62-20157, Italy
SOURCE: British Journal of Cancer (2003), 89(4), 763-773
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cytotoxic effect of aplidine was investigated on fresh leukemia cells derived from children with B-cell-precursor (BCP) acute lymphoblastic leukemia (ALL) by using stromal-layer culture system and on four cell lines, ALL-PO, Reh, ALL/MIK and TOM-1, derived from patients with ALL with different mol. genetic abnormalities. In ALL cell lines aplidine was cytotoxic at nanomolar concns. In the ALL cell lines the drug-induced cell death was clearly related to the induction of apoptosis and appeared to be p53-independent. Only in ALL-PO 20 nM aplidine treatment caused a block of vascular endothelial growth factor (VEGF) secretion and down-regulation of VEGF-mRNA, but aplidine cytotoxicity does not seem to be related to VEGF inhibition since the sensitivity of ALL-PO cells to aplidine is comparable to that observed for the other cells used. Aplidine induced a G1 and a G2 M block in ALL cell lines. In patient-derived leukemia cells, aplidine induced a strong cytotoxicity evidenced in a stroma-supported immunocytometric assay. Cells from children with genetic abnormalities such as t(9;22) and t(4;11) translocations, associated with an inferior treatment outcome, were sensitive to aplidine to the same extent as that observed in other BCP-ALL cases. Aplidine exerted a strong cell killing effect (>88%) against primary culture cells from five relapsed ALL cases, at concns. much lower than those reported to be achieved in plasma of patients receiving aplidine at recommended doses. Taken together these data suggest that aplidine could be a new anticancer drug to be investigated in ALL patients resistant to available therapy.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 21 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:584509 HCAPLUS
DOCUMENT NUMBER: 139:332249
TITLE: Validation of a sensitive assay for thiocoraline in mouse plasma using liquid chromatography-tandem mass spectrometry
AUTHOR(S): Yin, Jianming; Aviles, Pablo; Lee, William; Ly, Carl; Guillen, Maria Jose; Calvo, Pilar; Manzanares, Ignacio; Faircloth, Glynn
CORPORATE SOURCE: PharmaMar USA, Inc., Cambridge, MA, 02139-4616, USA
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2003), 794(1), 89-98
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive HPLC-tandem mass spectrometry assay for thiocoraline, an antitumor depsipeptide, in mouse plasma is described. Echinomycin, a quinoxaline peptide, was used as an internal standard Thiocoraline was recovered from the mouse plasma using protein precipitation with MeCN and followed by solid-phase extraction of the supernatant. The mobile phase consisted of MeOH (0.1% formic acid)-H2O (0.1% formic acid) (90:10, volume/volume). The anal. column was a YMC C18. The standard curve was linear from 0.1 to 50 ng/mL (R2>0.99). The lower limit of quantitation was 0.1 ng/mL. The assay was specific based on the multiple reaction monitoring transitions at m/z 1157 → 215 and m/z 1101 → 243 for thiocoraline and the internal standard, echinomycin, resp. The mean intra- and inter-day assay accuracies remained <5 and 12%, resp., for all calibration stds. and quality control (QC) samples. The intra- and inter-day assay precisions were <11.4 and 9.5% for all QC levels, resp. The utility of the assay was demonstrated by a pharmacokinetic study of i.v. (bolus) thiocoraline on CD-1 mice. Thiocoraline was stable in mouse plasma in an ice-water bath for 6 h and for three freeze-thaw cycles. The reconstituted thiocoraline after extraction and drying sample process was stable in the autosampler for over 24 h. The assay was able to quantify thiocoraline in plasma up to 48 h following dose. Pharmacokinetic anal. showed that thiocoraline has distinct pharmacokinetic profiling when dosed in different formulation solns. The assay is currently used to measure thiocoraline plasma concns. in support of a project to develop a suitable formulation with a desirable pharmacokinetic profile.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 22 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:548630 HCAPLUS
DOCUMENT NUMBER: 140:174525
TITLE: Effective combination of ET-743 and doxorubicin in sarcoma: preclinical studies
AUTHOR(S): Meco, Daniela; Colombo, Tina; Ubezio, Paolo; Zucchetti, Massimo; Zaffaroni, Marco; Riccardi, Anna; Faircloth, Glynn; Jose, Jimeno; D'Incalci, Maurizio; Riccardi, Riccardo
CORPORATE SOURCE: Division of Pediatric Oncology, Catholic University of Rome, Rome, Italy
SOURCE: Cancer Chemotherapy and Pharmacology (2003), 52(2), 131-138
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study was to investigate the cytotoxic and antitumor effects of the combination of the novel anticancer drug ET-743 and doxorubicin (Dx) and to determine whether any pharmacokinetic interaction occurs in sarcoma-bearing mice. The cytotoxicity of each drug and of their combinations was assessed in the rhabdomyosarcoma cell line TE-671 by a clonogenic assay, and isobologram anal. was performed to detect any synergistic, additive or antagonistic effects. The antitumor activities of each drug and of the combinations were also evaluated in nude mice transplanted s.c. with human TE-671 rhabdomyosarcoma and in C3H female mice injected i.v. with UV2237 M fibrosarcoma or with the Dx-resistant subline UV2237 M-ADM which over-expresses Pgp. Antitumor activity was evaluated by monitoring the TE-671 tumor volume over time and, in the case of the murine fibrosarcomas, by evaluation of lung deposits at autopsy quantified by determining lung weight Pharmacokinetic studies were performed in TE-671-bearing mice. ET-743 was determined in plasma by an HPLC-MS method and Dx in plasma and tissue by an HPLC method with fluorescence detection. The combination of ET-743 and Dx was found to be additive with the average combination index slightly lower than 1 at all survival levels, suggesting weak synergism. In TE-671 tumors in vivo the activity of ET-743 or Dx given alone was marginal, whereas the combination produced a significant antitumor effect. The log cell kill (LCK) values were 0.13 and 0.33 for ET-743 and Dx alone, whereas they ranged from 0.85 to 1.12 for the combination. Giving ET-743 1 h before Dx slightly enhanced the effect (LCK 1.12) compared with giving the drugs simultaneously (LCK 0.85) or in the opposite sequence (LCK 0.92). In UV2237 M fibrosarcoma, both Dx and ET-743 showed an effect in reducing the weight of lung metastases, although the combination of the two drugs was not superior to each drug alone. In UV2237 M-ADM tumors neither of the two drugs was active, whereas the combination, particularly when the two drugs were given simultaneously, produced a significant effect. Plasma levels of ET-743 and Dx were not significantly different when the drugs were given alone or in combination. The concns. of Dx in tissues including tumor, liver, heart and kidney were found to be the same whether the drug was given alone or in combination with ET-743. These results indicate that ET-743 and Dx in combination produce an additive effect against human sarcoma cells, reinforcing the idea that they act by a different mechanism of action. In mice no pharmacokinetic interaction between the two drugs was found. The observed activity in UV2237 M-ADM and in human TE-671 sarcoma suggests that the combination of the two drugs could be effective for tumors displaying low sensitivity to each drug given alone. Based on these findings a phase I study on the combination of the two drugs was recently initiated.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 23 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:493914 HCAPLUS

DOCUMENT NUMBER: 140:35427

TITLE: In vitro cytotoxicity of aplidin and crossresistance with other cytotoxic drugs in childhood leukemic and normal bone marrow and blood samples: a rational basis for clinical development

AUTHOR(S): Bresters, D.; Broekhuizen, A. J. F.; Kaaijk, P.; Faircloth, G. T.; Jimeno, J.; Kaspers, G. J. L.

CORPORATE SOURCE: Department of Pediatric Hematology/Oncology, VU University Medical Center, Amsterdam, 1081, Neth.

SOURCE: Leukemia (2003), 17(7), 1338-1343
CODEN: LEUKED; ISSN: 0887-6924
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To determine the potential of aplidin as a cytotoxic agent in pediatric leukemia, we tested bone marrow (BM) and peripheral blood (PB) samples (n=72) of children with different types of leukemia and healthy children in the methyl-thiazol-tetrazolium assay. Also, we compared these results with other cytotoxic drugs. Aplidin was cytotoxic in vitro at nanomolar concns., in a dose-dependent fashion. L-carnitine, that is applied in clin. studies to prevent myotoxicity caused by aplidin, had no effect on aplidin cytotoxicity in vitro. Aplidin cytotoxicity in vitro was not different when initial and relapsed acute lymphoblastic leukemia (ALL) or initial ALL and initial acute myeloid leukemia were compared. However, normal BM (n=19) and PB (n=13) cells were more resistant to aplidin than leukemic cells (median two- to seven-fold, P=0.001 and median four- to 11-fold, P<0.0001, resp.). In leukemia samples, no significant crossresistance between aplidin and other cytotoxic drugs was found, except for a trend for correlation with 2',2'-difluorodeoxycytidine (ρ=0.71, P=0.02). In normal BM samples, significant crossresistance with the epipodophyllotoxins was found, which is not readily explained by the currently known mechanisms of action of aplidin. In conclusion, we show that aplidin has selective cytotoxicity in vitro towards childhood leukemia cells and generally lacks crossresistance with other known cytotoxic drugs, which warrants clin. studies. Leukemia (2003) 17, 1338-1343.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 24 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:196182 HCAPLUS
DOCUMENT NUMBER: 139:285666
TITLE: Antiangiogenesis Treatment Combined with Chemotherapy Produces Chondrosarcoma Necrosis
AUTHOR(S): Morioka, Hideo; Weissbach, Lawrence; Vogel, Tikva; Nielsen, G. Petur; Faircloth, Glynn T.; Shao, Li; Hornicek, Francis J.
CORPORATE SOURCE: Orthopedic Research Laboratories, Harvard Medical School, Boston, MA, 02114, USA
SOURCE: Clinical Cancer Research (2003), 9(3), 1211-1217
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A combination therapy protocol using a marine chemotherapeutic and antiangiogenic mol. was tested in a mouse tumor xenograft model for the ability to curtail the growth of a human chondrosarcoma (CHSA). Ecteinascidin-743 (ET-743), a marine-derived chemotherapeutic, was effective at slowing the growth of a primary CHSA. Plasminogen-related protein B, which antagonizes various endothelial cell activities, also elicited a significant inhibition of neoplastic growth, albeit with reduced effectiveness. The combination of the two agents resulted in only a modest further repression of tumor growth over that associated with ET-743 treatment alone, as measured by tumor volume (82% vs. 76% inhibition, resp.). However, anal. of the extent of tumor necrosis and vascularization of the tumor revealed that the coadministration of the two compds. was clearly more effective, eliciting a 2.5-fold increase in tumor necrosis relative to single-agent treatment. The combination therapy also was most effective

at antagonizing tumor-associated microvessel formation, as assessed by CD31 immunostaining, suggesting that combination therapy may hold promise for treating CHSA. Tumor necrosis produced by combination therapy of ET-743 and recombinant plasminogen-related protein B was also significantly greater than that produced by conventional doxorubicin treatment, further corroborating the efficacy of combination therapy.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 25 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:96560 HCAPLUS
DOCUMENT NUMBER: 139:207206
TITLE: Changes in gene expression profile induced by the anticancer agent Aplidine in Molt-4 leukemic cell lines
AUTHOR(S): Marchini, S.; Chiorino, G.; Faircloth, G. T. ; D'Incalci, M.
CORPORATE SOURCE: Department of Oncology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
SOURCE: Journal of Biological Regulators and Homeostatic Agents (2002), 16(3), 241-248
CODEN: JBRAER; ISSN: 0393-974X
PUBLISHER: Wichtig Editore
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Microarray technique was employed to study differences in gene expression profile induced by Aplidine treatment in the Molt-4 human leukemic T cell line. Aplidine is a novel marine compound purified from caribbean tunicate (sea squirt) Aplidium albicans. Despite promising antitumor activity, few data are available on its mechanism of action. Exponentially growing cells were treated with Aplidine concns. close to its IC50 for 1 h and RNA samples collected after 0.5, 1, 6 and 24 h of recovery in drug free medium. The 32P labeled cDNAs were hybridized against Atlas Human Cancer arrays onto which 588 cDNAs were spotted. Genes involved in different cellular pathways, (such as growth factors, signal transduction or transcription factors) were found modulated by the drug. Even if the data obtained in the present study cannot be conclusive, several hypothesis on Aplidine's mechanism of action are indicated that will be the subject of future studies.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 26 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:35878 HCAPLUS
DOCUMENT NUMBER: 139:223836
TITLE: Aplidine, a new anticancer agent of marine origin, inhibits vascular endothelial growth factor (VEGF) secretion and blocks VEGF-VEGFR-1 (flt-1) autocrine loop in human leukemia cells MOLT-4
AUTHOR(S): Broggini, M.; Marchini, S. V.; Galliera, E.; Borsotti, P.; Taraboletti, G.; Erba, E.; Sironi, M.; Jimeno, J.; Faircloth, G. T.; Giavazzi, R.; D'Incalci, M.
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Istituto di Ricerche Farmacologiche Mario Negri', Milan, Italy
SOURCE: Leukemia (2003), 17(1), 52-59
CODEN: LEUKED; ISSN: 0887-6924
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism by which aplidine, a marine natural product in early clin. development as an anticancer agent, induces cell growth inhibition and apoptosis has been investigated in the human leukemia cell line MOLT-4. This cell line is characterized not only by the ability to secrete VEGF, but also for the presence on its surface of the VEGF receptor-1 (VEGFR-1). Previous studies from our laboratory concerned with evaluating early changes in gene expression induced by aplidine in MOLT-4 cells have shown that the drug decreases the expression of VEGFR-1 (Marchini et al., 2000). Here, we report the ability of aplidine to block the VEGF/VEGFR-1 loop. We found that aplidine blocked VEGF secretion that was temporally followed by a decrease in both VEGF and VEGFR-1 production Aplidine did not directly affect either VEGF transcription or stabilization of its mRNA. Transfection of MOLT-4 cells with an antisense VEGF cDNA construct, resulted in inhibition of colony formations. One clone, transfected with sense VEGF cDNA, secreting 8-10 times more VEGF than parental cells, was less sensitive to aplidine-induced cytotoxicity and apoptosis than control cells. Moreover, addition of VEGF in the medium decreased the activity of aplidine in MOLT-4 cells. These data demonstrate that aplidine inhibits the growth and induces apoptosis in MOLT-4 cells through the inhibition of VEGF secretion which blocks the VEGF/VEGFR-1 autocrine loop necessary for the growth of these cells.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 27 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:974072 HCAPLUS

DOCUMENT NUMBER: 139:127523

TITLE: Effectiveness of ecteinascidin-743 against drug-sensitive and -resistant bone tumor cells

AUTHOR(S): Scotlandi, Katia; Perdichizzi, Stefania; Manara, Maria Cristina; Serra, Massimo; Benini, Stefania; Cerisano, Vanessa; Strammiello, Rosaria; Mercuri, Mario; Reverter-Branchat, Gemma; Faircloth, Glynn; D'Incalci, Maurizio; Picci, Piero

CORPORATE SOURCE: Laboratorio di Ricerca Oncologica, Istituti Ortopedici Rizzoli, Bologna, 40136, Italy

SOURCE: Clinical Cancer Research (2002), 8(12), 3893-3903
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The identification of new drugs is strongly needed for bone tumors . Ecteinascidin-743 (ET-743), a highly promising antitumor agent isolated from the marine tunicate Ecteinascidia turbinata, is currently under Phase II clin. investigation in Europe and the United States for treatment of soft tissue sarcoma. In this study, we analyzed the preclin. effectiveness of this drug in osteosarcoma and Ewing's sarcoma. The effects of ET-743 were evaluated against a panel of human osteosarcoma and Ewing's sarcoma cell lines characterized by different drug responsiveness and compared with the effects of standard anticancer agents. In addition, combination treatments with ET-743 and the other standard chemotherapy agents for sarcoma were analyzed to highlight the best drug-to-drug interaction. A potent activity of ET-743 was clearly observed against both drug-sensitive and drug-resistant (multidrug-resistant, methotrexate- and cisplatin-resistant) bone tumor cells at concns. that are easily achievable in patients (pM to nM range). Ewing's sarcoma cells appeared to be particularly sensitive to the effects of this drug. The anal. of the effects of ET-743 on cell cycle, apoptosis, and differentiation indicated that both osteosarcoma and

Ewing's sarcoma cells had a slower progression through the different phases of the cell cycle after treatment with ET-743. However, the drug was able to induce a massive apoptosis in Ewing's sarcoma but not in osteosarcoma cells. In the latter neoplasm, ET-743 showed a differential effect, as indicated by the significant increase in the expression and activity of alkaline phosphatase, a marker of osteoblastic differentiation. Concurrent exposure of cells to ET-743 and other chemotherapeutic agents resulted in greater than additive interactions when doxorubicin and cisplatin were used, whereas subadditive effects were observed with methotrexate, vincristine, and actinomycin D. Overall, these results encourage the inclusion of this drug in the treatment of patients with bone tumors, although a careful design of new regimens is required to identify the best therapeutic conditions.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 28 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:526235 HCAPLUS
DOCUMENT NUMBER: 138:100185
TITLE: Unique features of the mode of action of ET-743
AUTHOR(S): D'Incalci, Maurizio; Erba, Eugenio; Damia, Giovanna; Galliera, Emanuela; Carrassa, Laura; Marchini, Sergio; Mantovani, Roberto; Tognon, Gianluca; Fruscio, Robert; Jimeno, Jose; Faircloth, Glynn T.
CORPORATE SOURCE: Department of Oncology, Istituto di Ricerche Farmacologiche "Mario Negri,", Milan, 20157, Italy
SOURCE: Oncologist (2002), 7(3), 210-216
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review of the current knowledge of the primary mode of action of a natural product, ecteinascidin 743 (ET-743), derived from the marine tunicate Ecteinascidia turbinata. ET-743 was initially selected for preclin. development because of its potent antitumor activity observed against several human solid tumor types. In vitro, the drug is cytotoxic in the nanomolar range, and in the case of some very sensitive cell lines, in the picomolar range. The large potency differences observed among several solid tumor types indicate that this compound possesses some tumor selectivity, but the mol. basis of these differential effects remains to be elucidated. The the mechanism of action of ET-743 is evaluated in this context. The available information on ET-743 binding to DNA and its effects on transcriptional regulation point to a unique behavior of this drug, as it independently affects specific gene transcription in a promoter-dependent way. In addition, ET-743 shows a peculiar pattern of selectivity in cells with different defects in their DNA-repair pathways. These results highlight a unique property of ET-743, possibly explaining why it possesses antitumor activity against tumors that are refractory to standard anticancer drugs, all of which certainly act by mechanisms that are different from that of ET-743.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 29 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:486038 HCAPLUS
DOCUMENT NUMBER: 138:66278
TITLE: Cell cycle phase perturbations and apoptosis in tumour cells induced by aplidine
AUTHOR(S): Erba, E.; Bassano, L.; Di Liberti, G.; Muradore, I.;

Chiorino, G.; Ubezio, P.; Vignati, S.; Codegoni, A.; Desiderio, M. A.; Faircloth, G.; Jimeno, J.; D'Incalci, M.
CORPORATE SOURCE: Cancer Pharmacology Laboratory, Department of Oncology, Instituto di Richerche Farmacologiche Mario Negri, Milan, 20157, Italy
SOURCE: British Journal of Cancer (2002), 86(9), 1510-1517
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aplidine, dehydrodidemnin B, is a marine depsipeptide isolated from the Mediterranean tunicate Aplidium olbicans currently in phase II clin. trial. In human Molt-4 leukemia cells aplidine was found to be cytotoxic at nanomolar concns. and to induce both a G1 arrest and a G2 blockade. The drug-induced cell cycle perturbations and subsequent cell death do not appear to be related to macromol. synthesis (protein, RNA, DNA) since the effects occur at concns. (e.g. 10 nM) in which macromol. synthesis was not markedly affected. Ten nM Aplidine for 1 h inhibited Orn decarboxylase activity, with a subsequently strong decrease in putrescine levels. This finding has questionable relevance since addition of putrescine did not significantly reduce the cell cycle perturbations or the cytotoxicity of aplidine. The cell cycle perturbations caused by aplidine were also not due to an effect on the cyclin-dependent kinases. Although the mechanism of action of aplidine is still unclear, the cell cycle phase perturbations and the rapid induction of apoptosis in Molt-4 cells appear to be due to a mechanism different from that of known anticancer drugs.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 30 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:476181 HCAPLUS
DOCUMENT NUMBER: 138:180273
TITLE: In vitro toxicity of ET-743 and Aplidine, two marine-derived antineoplastics, on human bone marrow hematopoietic progenitors comparison with the clinical results
AUTHOR(S): Albella, B.; Faircloth, G.; Lopez-Lazaro, L.; Guzman, C.; Jimeno, J.; Bueren, J. A.
CORPORATE SOURCE: Department of Molecular and Cellular Biology, CIEMAT, Madrid, 28040, Spain
SOURCE: European Journal of Cancer (2002), 38(10), 1395-1404
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ecteinascidine-743 (ET-743) and Aplidine are 2 marine-derived antineoplastics currently in phase II development. With the aim of evaluating whether in vitro hematopoietic studies can predict the toxicity of these 2 drugs in patients, human bone marrow (BM) samples were incubated with these drugs under conditions which mimicked the administration exposures used in the clinics. As it was observed in different cancer cell lines, ET-743 was more toxic on an equimolar basis in human hematopoietic progenitors (inhibitory concentration reducing the viability to 50% after 24-h exposures; IC5024h: 10-50 nM) compared with doxorubicin (IC5024h values: 280-460 nM), used as a control anticancer drug. In contrast to the high hematotoxic effects observed for ET-743, similar IC values were obtained for Aplidine (IC5024h: 150-530 nM) compared with doxorubicin. For both ET-743 and Aplidine, the megakaryocytic progenitor was the most sensitive, compared with the other

hematopoietic progenitors (IC50 values were 3- to 5-fold lower in the CFU-Megs compared with the CFU-GMs). The observation that the Cmax observed in patients treated with the Aplidine maximum tolerated dose (MTD) (7.1 nM) was 21-75-fold lower than the IC5024h value observed for the different hematopoietic progenitors is highly consistent with the lack of hematotoxicity observed in patients treated with this drug. In the case of ET-743, differences between the Cmax value corresponding to the MTD (2.6 nM) and the in vitro IC50 values corresponding to the different progenitors were much lower (4-19-fold), also consistent with the hematotoxicity that was observed in patients treated at recommended doses (RDs) and MTDs. Although CFU-Megs were more sensitive than CFU-GM progenitors to ET-743 in vitro, clin. data showed that neutropenic events were more frequent than thrombocytopenic episodes. Aiming to further improve the predictive value of in vitro IC values corresponding to the different hematopoietic progenitors, addnl. refinement parameters derived from pharmacokinetic and animal studies are proposed.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 31 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:817226 HCAPLUS
DOCUMENT NUMBER: 135:362533
TITLE: Immunosuppressive sesbanimide compositions
INVENTOR(S): Faircloth, Glynn T.; Millan, Francisco Romero; Fernandez, Librada Maria Canedo; Sarabia, Cristina Accbal
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont. of U.S. Ser. No. 53,485, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001039041	A1	20011108	US 2001-756244	20010108
PRIORITY APPLN. INFO.:			US 1995-479695	B1 19950607
			US 1998-53485	B1 19980401

AB The active component of the pharmaceutical composition of the present invention is a compound which has been isolated from the controlled aerobic fermentation of a marine microorganism, Agrobacterium sp. The pharmaceutical compns. of the present invention, useful for postsurgical graft tolerance, are thus directed to compns. comprising a pharmaceutical carrier, diluent or excipient, and an effective amount of sesbanimide, which is an alkaloid that has been previously been isolated from seeds and reported to be useful as an antitumor drug. Prior to the present invention however, this compound had not been isolated from any fermentation broth nor had it been determined to have immunomodulatory activity. The crude residue of fermented Agrobacterium species was dissolved in H2O-MeOH (1:1). The water/alc. fraction was extracted twice with CH2Cl2 and twice with EtOAc. The organic solvent-soluble components were concentrated yielding active organic exts. The organic extract was chromatographed on silica gel by an MPLC system using a mixture of hexane/EtOAc as the eluting solvent. The immunosuppressive and antitumor activities were detected in some of the fractions.

L20 ANSWER 32 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:750175 HCAPLUS
DOCUMENT NUMBER: 136:395455
TITLE: Sensitivity of soft tissue sarcoma cell lines to chemotherapeutic agents: identification of ecteinascidin-743 as a potent cytotoxic agent
AUTHOR(S): Li, Wei Wei; Takahashi, Naoto; Jhanwar, Suresh; Cordon-Cardo, Carlos; Elisseyeff, Yaroslav; Jimeno, Jose; Faircloth, Glynn; Bertino, Joseph R.
CORPORATE SOURCE: Laboratories of Molecular Pharmacology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Clinical Cancer Research (2001), 7(9), 2908-2911
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cytotoxic effects of ecteinascidin-743(ET-743), a novel marine natural product, were evaluated and compared with that of clin. used anticancer agents methotrexate, doxorubicin, etoposide, and paclitaxel in eight human soft tissue sarcoma (STS) cell lines. HT-1080, a fibrosarcoma cell line, and HS-42, a malignant mesodermal cell line, were the most sensitive of the cell lines to methotrexate, doxorubicin, etoposide, and paclitaxel. Other cell lines (IC50s) varied considerably and were more resistant to these agents. ET-743 was more potent than any of these agents, with IC50s in the PM range in all of the cell lines. Cytotoxicity of ET-743 was dose- and time-related (4-72 h exposure). Cytotoxic concns. of ET-743 produced a S/G2 block in all of the cell lines tested. Three colon adenocarcinoma cell lines, HCT-8, HT-29, and HCT-116, and one breast cancer cell line, MCF-7, were 1-2 logs less sensitive to ET-743 than the STS cell lines. Cell lines were also characterized as to expression of oncogenes and tumor suppressor genes to attempt to correlate sensitivity of these cell lines to ET-743 and other chemotherapeutic agents. All of the cell lines except M8805, a malignant fibrous histiocytoma cell line, had mutations in p53 and/or overexpressed the MDM2 protein. Only HS-18, a liposarcoma cell line, lacked expression of the retinoblastoma protein. None of the cell lines had detectable expression of P-glycoprotein as measured by immunohistochem. ET-743 is an extremely potent cytotoxic agent against human STS cell lines and is being evaluated as an antitumor agent in this disease.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 33 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:688131 HCAPLUS
DOCUMENT NUMBER: 136:48209
TITLE: In vitro hematotoxicity of Aplidine on human bone marrow and cord blood progenitor cells
AUTHOR(S): Gomez, S. G.; Faircloth, G.; Lopez-Lazaro, L.; Jimeno, J.; Bueren, J. A.; Albella, B.
CORPORATE SOURCE: Department of Molecular and Cellular Biology, CIEMAT, Madrid, 28040, Spain
SOURCE: Toxicology in Vitro (2001), 15(4/5), 347-350
CODEN: TIVIEQ; ISSN: 0887-2333
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aplidine is a cyclic depsipeptide that was isolated from a Mediterranean marine tunicate, Aplidium albicans. In exptl. animals, Aplidine mediated

an in vivo inhibitory effect in a number of tumor cell types. In humans, Aplidine is currently used in phase I clin. trials. Aiming to predict the hematotoxicity of Aplidine in humans, samples from human bone marrow (BM) and cord blood (CB) were exposed in vitro to increasing concns. of the drug and then assayed for the clonogenic ability of myeloid (CFU-GM), erythroid (BFU-E), megakaryocytic (CFU-Meg) and pluripotent (CFU-Mix) hematopoietic progenitors. We investigated whether predictions of the hematotoxicity of Aplidine based on bone marrow (BM) cultures were reproduced when a more readily available source of human hematopoietic cells, cord blood cells, was used in expts. involving 24-h exposures. Although hematopoietic progenitors derived from bone marrow were generally more sensitive than those derived from cord blood, differences on the IC50, IC70 and IC90 varied within a relatively small range of 1.6-6.2-fold. Moreover, data obtained from cord blood cultures confirmed the observation made in bone marrow assays indicating that the myeloid (CFU-GM) and the erythroid (BFU-E) progenitors were the least sensitive to Aplidine. Regardless of the origin of the hematopoietic progenitors (bone marrow or cord blood) the toxicity of Aplidine in human hematopoietic progenitors (IC50: 150-2250 nm) was lower than that observed in previous studies with tumoral cell lines.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 34 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:380410 HCAPLUS
DOCUMENT NUMBER: 134:361352
TITLE: Aplidine for treatment of cancers
INVENTOR(S): Faircloth, Glynn Thomas; Twelves, Chris; Paz-Ares, Luis
PATENT ASSIGNEE(S): Pharma Mar S.A., Spain
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035974	A2	20010525	WO 2000-GB4349	20001115
WO 2001035974	A3	20011101		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2391502	AA	20010525	CA 2000-2391502	20001115
BR 2000015811	A	20020806	BR 2000-15811	20001115
EP 1229922	A2	20020814	EP 2000-976137	20001115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003514025	T2	20030415	JP 2001-537965	20001115
NZ 518847	A	20040227	NZ 2000-518847	20001115
AU 780417	B2	20050317	AU 2001-14023	20001115
RU 2261104	C2	20050927	RU 2002-115864	20001115
CA 2424823	AA	20020418	CA 2001-2424823	20011012

WO 2002030441	A2	20020418	WO 2001-GB4555		20011012
WO 2002030441	A3	20020801			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2001094024	A5	20020422	AU 2001-94024		20011012
EP 1330254	A2	20030730	EP 2001-974510		20011012
EP 1330254	B1	20050706			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2001014604	A	20031014	BR 2001-14604		20011012
JP 2004510824	T2	20040408	JP 2002-533881		20011012
NZ 525196	A	20040924	NZ 2001-525196		20011012
AT 299028	E	20050715	AT 2001-974510		20011012
ES 2243555	T3	20051201	ES 2001-1974510		20011012
AU 2001294024	B2	20060105	AU 2001-294024		20011012
NO 2002002293	A	20020705	NO 2002-2293		20020514
BG 106714	A	20030228	BG 2002-106714		20020518
NO 2003001673	A	20030612	NO 2003-1673		20030411
US 2004010043	A1	20040115	US 2003-398835		20030801
PRIORITY APPLN. INFO.:			GB 1999-27006	A	19991115
			GB 2000-5701	A	20000309
			GB 2000-7639	A	20000329
			GB 2000-15496	A	20000623
			GB 2000-25209	A	20001013
			GB 2000-25044	A	20001012
			WO 2000-GB4349	W	20001115
			GB 2001-7373	A	20010323
			WO 2001-GB4555	W	20011012

AB Aplidine demonstrates considerable promise in phase I clin. trials for treatment of tumors, and various dosing regimes are given. Tumor reduction has been observed in several tumor types including renal carcinoma, colorectal cancer, lung carcinoid, medullary thyroid carcinomas and melanoma. It has also been found that aplidine has a role in inhibiting angiogenesis, complementing the antitumor activity.

L20 ANSWER 35 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:363160 HCAPLUS
DOCUMENT NUMBER: 136:130300
TITLE: Unique pattern of ET-743 activity in different cellular systems with defined deficiencies in DNA-repair pathways
AUTHOR(S): Damia, Giovanna; Silvestri, Simonetta; Carrassa, Laura; Filiberti, Laura; Faircloth, Glynn T. ; Liberi, Giordano; Foiani, Marco; D'Incalci, Maurizio
CORPORATE SOURCE: Department of Oncology, Instituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy
SOURCE: International Journal of Cancer (2001), 92(4), 583-588 CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cytotoxic activity of ecteinascidin 743 (ET-743), a natural product

derived from the marine tunicate Ecteinascidia turbinata that exhibits potent anti-tumor activity in pre-clin. systems and promising activity in phase I and II clin. trials, was investigated in a number of cell systems with well-defined deficiencies in DNA-repair mechanisms. ET-743 binds to N2 of guanine in the minor groove, but its activity does not appear to be related to DNA-topoisomerase I poisoning as the drug is equally active in wild-type yeast and in yeast with a deletion in the DNA-topoisomerase I gene. Defects in the mismatch repair pathway, usually associated with increased resistance to methylating agents and cisplatin, did not affect the cytotoxic activity of ET-743. However, ET-743 did show decreased activity (from 2- to 8-fold) in nucleotide excision repair (NER)-deficient cell lines compared to NER-proficient cell lines, from either hamsters or humans. Restoration of NER function sensitized cells to ET-743 treatment. The DNA double-strand-break repair pathway was also investigated using human glioblastoma cell lines MO59K and MO59J, resp., proficient and deficient in DNA-dependent protein kinase (DNA-PK), ET-743 was more effective in cells lacking DNA-PK; moreover, pre-treatment of HCT-116 colon carcinoma cells with wortmannin, a potent inhibitor of DNA-PK, sensitized cells to ET-743. An increase in ET-743 sensitivity was also observed in ataxia telangiectasia-mutated cells. The data strongly suggest that ET-743 has a unique mechanism of interaction with DNA.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 36 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:73747 HCAPLUS
DOCUMENT NUMBER: 135:116666
TITLE: Ecteinascidin-743 (ET-743), a natural marine compound, with a unique mechanism of action
AUTHOR(S): Erba, E.; Bergamaschi, D.; Bassano, L.; Damia, G.; Ronzoni, S.; Faircloth, G. T.; D'Incalci, M.
CORPORATE SOURCE: Istituto di Ricerche Farmacologiche 'Mario Negri', Department of Oncology, Milan, 20157, Italy
SOURCE: European Journal of Cancer (2001), 37(1), 97-105
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mode of action of Ecteinascidin-743 (ET-743), a marine tetrahydroisoquinoline alkaloid isolated from Ecteinascidia turbinata, which has shown very potent antitumor activity in preclin. systems and encouraging results in Phase I clin. trials was investigated at a cellular level. Both SW620 and LoVo human intestinal carcinoma cell lines exposed for 1 h to ET-743 progress through S phase more slowly than control cells and then accumulate in the G2M phase. The sensitivity to ET-743 of G1 synchronized cells was much higher than that of cells synchronized in S phase and even higher than that of cells synchronized in G2M. ET-743 concns. up to four times higher than the IC50 value caused no detectable DNA breaks or DNA-protein cross-links as assessed by alkaline elution techniques. ET-743 induced a significant increase in p53 levels in cell lines expressing wild-type (wt) (p53). However, the p53 status does not appear to be related to the ET-743 cytotoxic activity as demonstrated by comparing the drug sensitivity in p53 (-/-) or (+/+) mouse embryo fibroblasts and in A2780 ovarian cancer cells or the A2780/CX3 sub-line transfected with a dominant-neg. mutant TP53. The cytotoxic potency of ET-743 was comparatively evaluated in CHO cell lines proficient or deficient in nucleotide excision repair (NER), and it was found that ET-743 was approx. 7-8 times less active in ERCC3/XPB and ERCC1-deficient cells than control cells. The findings that G1 phase cells are hypersensitive and that NER-deficient cells are resistant to

ET-743 indicate that the mode of action of ET-743 is unique and different from that of other DNA-interacting drugs.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 37 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:412188 HCAPLUS
DOCUMENT NUMBER: 133:129636
TITLE: Interference of transcriptional activation by the antineoplastic drug ecteinascidin-743
AUTHOR(S): Minuzzo, Mario; Marchini, Sergio; Broggini, Massimo; Faircloth, Glynn; D'Incalci, Maurizio; Mantovani, Roberto
CORPORATE SOURCE: Dipartimento di Genetica e di Biologia dei Microrganismi, Universita degli Studi di Milano, Milan, 20133, Italy
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(12), 6780-6784 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ecteinascidin-743 (ET-743) is a tetrahydroisoquinoline alkaloid isolated from the tunicate Ecteinascidia turbinata currently under phase II clin. trials for its potent anticancer activity. ET-743 binds DNA in the minor groove and forms covalent adducts with some sequence specificity. It selectively inhibits in vitro binding of the CCAAT box factor NF-Y. In this study, the authors assayed ET-743 function in vivo on the HSP70 promoter. On heat induction, the drug blocks transcription rapidly at pharmacol. concns. and in a CCAAT-dependent manner, whereas the activity of the CCAAT-less simian virus 40 promoter is not affected. The effect is exerted at the mRNA level. The distamycin-like alkylating tallimustine is inactive in these assays. Binding of NF-Y and of the heat-shock factor is normal in ET-743-treated cells. Run-on anal. of several endogenous genes further proves that the drug has rapid, profound, and selective neg. effects on transcription. Thus, this marine-derived compound is a promoter-specific, transcription-interfering agent.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 38 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:412185 HCAPLUS
DOCUMENT NUMBER: 133:129635
TITLE: Ecteinascidin 743, a transcription-targeted chemotherapeutic that inhibits MDR1 activation
AUTHOR(S): Jin, Shengkan; Gorfajn, Barbara; Faircloth, Glynn; Scotto, Kathleen W.
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Memorial Sloan-Kettering Cancer Center and the Weill Graduate School of Medical Sciences of Cornell University, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(12), 6775-6779 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ecteinascidin 743 (ET-743), a highly promising marine-based anti-tumor agent presently in phase II clin. trials, has been shown to interfere with the binding of minor-groove-interacting transcription

factors, particularly NF-Y, with their cognate promoter elements in vitro. The authors have shown that NF-Y is a central mediator of activation of transcription of the human P glycoprotein gene (MDR1) by a variety of inducers and that NF-Y functions by recruiting the histone acetyltransferase PCAF to the MDR1 promoter. In the present study, the authors tested whether ET-743 could block activation of the MDR1 promoter by agents that mediate their effect through the NF-Y/PCAF complex. The authors report that physiol. relevant concns. of ET-743 abrogate transcriptional activation of both the endogenous MDR1 gene and MDR1 reporter constructs by the histone deacetylase inhibitors as well as by UV light, with minimal effect on constitutive MDR1 transcription. Notably, this inhibition does not alter the promoter-associated histone hyperacetylation induced by histone deacetylase inhibitors, suggesting an in vivo mol. target downstream of NF-Y/PCAF binding. ET-743 is therefore the prototype for a distinct class of transcription-targeted chemotherapeutic agents and may be an efficacious adjuvant to the treatment of multidrug-resistant tumors.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 39 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:384338 HCAPLUS

DOCUMENT NUMBER: 133:217447

TITLE: Isolation and characterization of an IGROV-1 human ovarian cancer cell line made resistant to Ecteinascidin-743 (ET-743)

AUTHOR(S): Erba, E.; Bergamaschi, D.; Bassano, L.; Ronzoni, S.; Di Liberti, G.; Muradore, I.; Vignati, S.; Faircloth, G.; Jimeno, J.; D'Incalci, M.

CORPORATE SOURCE: Cancer Pharmacology Laboratory, Department of Oncology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 62-20157, Italy

SOURCE: British Journal of Cancer (2000), 82(10), 1732-1739
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Harcourt Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB By exposing Igrov-1 human ovarian cancer cells to increasing concns. of Ecteinascidin-743 (ET-743), either for a short or prolonged time, the authors obtained sublines resistant to ET-743 which overexpress Pgp. The most resistant clone (Igrov-1/25 ET) was evaluated for biol. and pharmacol. characterizations. The increased Pgp levels of Igrov-1/25 ET were not due to amplification of the mdr-1 gene but to increased mRNA levels. No increase in other multidrug resistance-related proteins such as MRP or LRP was observed in Igrov-1/25 ET. The IC50 values of ET-743 against Igrov-1/25 ET was approx. 50 times higher than the parental cell line. Resistance was not reversed while maintaining the cell line in drug-free medium for at least 24 mo. Igrov-1/25 ET was cross-resistant to doxorubicin and VP 16 while it was equally sensitive to L-PAM, MNNG, CPT, and only marginally less sensitive to Cis-DDP and oxaliplatin compared to the parental cell line. Igrov-1/25 ET exposed to doxorubicin retained this drug much less, mainly because of a more efficient drug efflux. The cyclosporine analog SDZ PSC-833 reversed the resistance of Igrov-1/25 ET to ET-743, without any enhancement of the drug activity against the parental Igrov-1 cell line. Igrov-1/25 ET exhibits typical features of cell lines overexpressing the mdr-1 gene and can be a potentially useful tool in selecting ET-743 non-cross-resistant analogs as well as to investigate methods to counteract resistance to this drug.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 40 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:221294 HCAPLUS
DOCUMENT NUMBER: 133:99203
TITLE: The marine compound spisulosine, an inhibitor of cell proliferation, promotes the disassembly of actin stress fibers
AUTHOR(S): Cuadros, R.; Montejo de Garcini, E.; Wandosell, F.; Faircloth, G.; Fernandez-Sousa, J. M.; Avila, J.
CORPORATE SOURCE: Centro de Biologia Molecular 'Severo Ochoa' (CSIC-UAM), Universidad Autonoma de Madrid, Madrid, 28049, Spain
SOURCE: Cancer Letters (Shannon, Ireland) (2000), 152(1), 23-29
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Spisulosine is a novel antiproliferative (antitumoral) compound of marine origin. In this work the mol. target for this toxic agent has been analyzed. In the presence of spisulosine, cultured cells change their morphol., first acquiring a fusiform morphol., and later becoming rounded without focal adhesions. Anal. of the cytoskeleton of treated cells indicate the absence of actin stress fibers.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 41 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:672566 HCAPLUS
DOCUMENT NUMBER: 131:295576
TITLE: Spisulosine compounds having antitumor activity
INVENTOR(S): Rinehart, Kenneth Lloyd; Fregeau, Nancy Louise; Warwick, Robert Arthur; Garcia Gravalos, Dolores; Avila, Jesus; Faircloth, Glynn Thomas
PATENT ASSIGNEE(S): The Board of Trustees of the University of Illinois, USA; Ruffles, Graham Keith
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9952521	A1	19991021	WO 1999-GB1091	19990409
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6107520	A	20000822	US 1998-58456	19980410
CA 2328126	AA	19991021	CA 1999-2328126	19990409
AU 9934321	A1	19991101	AU 1999-34321	19990409
AU 763981	B2	20030807		

BR 9910120	A	20001226	BR 1999-10120		19990409
TR 200002955	T2	20010122	TR 2000-200002955		19990409
EP 1069894	A1	20010124	EP 1999-915898		19990409
EP 1069894	B1	20050831			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002511410	T2	20020416	JP 2000-543131		19990409
NZ 507349	A	20021220	NZ 1999-507349		19990409
RU 2225710	C2	20040320	RU 2000-128037		19990409
AT 303139	E	20050915	AT 1999-915898		19990409
ES 2248995	T3	20060316	ES 1999-915898		19990409
NO 2000005052	A	20001207	NO 2000-5052		20001006
BG 104935	A	20010731	BG 2000-104935		20001109
PRIORITY APPLN. INFO.:			US 1998-58456	A	19980410
			US 1997-43326P	P	19970415
			US 1997-43599P	P	19970415
			WO 1999-GB1091	W	19990409

AB Investigation of the activity of exts. of the clam Spisula polynyma has led to antitumor long-chain, straight-chain alkane or alkene compds. which have a 2-amino group and a 3-hydroxy group.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 42 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:625555 HCAPLUS

DOCUMENT NUMBER: 131:317437

TITLE: Effect of ecteinascidin-743 on the interaction between DNA binding proteins and DNA

AUTHOR(S): Bonfanti, Marina; La Valle, Elisa; Faro, Jose-Maria Fernandez Sousa; Faircloth, Glynn; Caretti, Giuseppina; Mantovani, Roberto; D'Incalci, Maurizio

CORPORATE SOURCE: Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri, Milan, 20157, Italy

SOURCE: Anti-Cancer Drug Design (1999), 14(3), 179-186
CODEN: ACDDEA; ISSN: 0266-9536

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Ecteinascidin-743 (ET-743) is a tetrahydroisoquinoline alkaloid isolated from Ecteinascidia turbinata, a tunicate growing in mangrove roots in Caribbean. It has been shown to bind in the minor groove of DNA forming covalent adducts by reaction of the N2 of guanine with the carbinolamine moiety. We investigated ET-743 ability to inhibit the binding of different transcription factors to their consensus sequences by using gel shift assays. We have selected three types of factors: (i) oncogene products such as MYC, c-MYB and Maf; (ii) transcriptional activators regulated during the cell cycle as E2F and SRF; and (iii) general transcription factors such as TATA binding protein (TBP), Sp1 and NF-Y. We observed no inhibition of the binding of Sp1, Maf, MYB and MYC. Inhibition of DNA binding was observed for TBP, E2F, SRF at ET-743 concns. ranging from 50 to 300 μM. The inhibition of binding of NF-Y occurs at even lower concns. (i.e. 10-30 μM) when the recombinant subunits of NF-Y are preincubated with the drug, indicating that the inhibition of NF-Y binding does not require previous ET-743 DNA binding. Since NF-Y is a trimer containing two subunits with high resemblance to histones H2B and H2A, we have investigated the effect of ET-743 on nucleosome reconstitution. ET-743 caused a decrease of the nucleosomal band at 100 nM, with the complete disappearance of the band at 3-10 μM. These data suggest that the mode of action of this novel anticancer drug is related to its ability to modify the interaction between some DNA binding

proteins and DNA.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 43 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:566537 HCAPLUS
DOCUMENT NUMBER: 131:208780
TITLE: Cytotoxicity and neurocytotoxicity of new marine anticancer agents evaluated using in vitro assays
AUTHOR(S): Geldof, Albert A.; Mastbergen, Simon C.; Henrar, Roland E. C.; Faircloth, Glynn T.
CORPORATE SOURCE: Dep. Urology/Nuclear Med., Vrije Univ. Amsterdam, Amsterdam, 1007 MB, Neth.
SOURCE: Cancer Chemotherapy and Pharmacology (1999), 44(4), 312-318
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB New classes of anticancer drugs, isolated from marine organisms, were shown to possess cytotoxic activity against multiple tumor types. Aplidine, didemnin B, and isohomohalichondrin B (IHB), among the more promising antitumor candidates, were evaluated in the present study on a comparative basis in terms of their antiproliferative activity and neurotoxic effects in vitro. Using a panel of different human prostatic cancer cell lines (DU 145, PC-3, and LNCaP-FGC) the effects of aplidine, didemnin B, and IHB on tumor cell proliferation were tested in a colorimetric (XTT) assay and compared with the effects of vincristine, vinorelbine, and taxol. Under analogous in vitro conditions these drugs were also monitored for neurocytotoxic effects using a PC 12 cell line based model. Didemnin B and - especially aplidine were more effective in the inhibition of prostate cancer cell proliferation than vincristine, vinorelbine, or taxol at concentration levels between 5-50 pmol/mL. At these same concns., however, didemnin B and aplidine were also most potent in the in vitro neurotoxicity assays. IHB was found to exert even more potent antiproliferative activity (at concentration levels between 0.05-0.1 pmol/mL). However, neurotoxic effects were also found to be present at these levels. After drug withdrawal, the neurotoxic damage, inflicted by aplidine or IHB appeared to be more long lasting than after vincristine or vinorelbine exposure. These results point to high antiproliferative activity of aplidine and IHB in prostate cancer. At the same time, the data urge some caution in the clin. use of these agents because of potential neurotoxic side-effects. The use of a newly formulated aplidine may involve a more favorable therapeutic profile.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 44 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:432824 HCAPLUS
DOCUMENT NUMBER: 131:179198
TITLE: Bioanalysis of aplidine, a new marine antitumoral depsipeptide, in plasma by high-performance liquid chromatography after derivatization with trans-4'-hydrazino-2-stilbazole
AUTHOR(S): Sparidans, Rolf W.; Kettenes-Van Den Bosch, J. Jantien; Van Tellingen, Olaf; Nuyen, Bastiaan; Henrar, Roland E. C.; Jimeno, Jose M.; Faircloth,

Glynn; Floriano, Pablo; Rinehart, Kenneth L.; Beijnen, Jos H.
CORPORATE SOURCE: Faculty of Pharmacy, Department of Pharmaceutical Analysis, Utrecht University, Utrecht, 3584 CA, Neth.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 729(1 + 2), 43-53
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive bio-anal. assay in plasma of the depsipeptide aplidine is reported, based on reversed-phase liquid chromatog. and fluorescence detection of the trans-4'-hydrazino-2-stilbazole (4'H2S) derivative of the analyte. At ambient temperature, two conformations of the depsipeptide are observed in solution due to cis-trans isomerism at the proline-pyruvoyl peptide bond. Aplidine is isolated from the matrix by solid-phase extraction on an octadecyl modified silica stationary phase. After evaporation of the acetone eluate, a derivatization with 4'H2S is performed in a water-acetonitrile mixture at pH 4. The reaction mixture is injected directly into the chromatograph and the analyte is quantified by fluorescence detection at 410 and 560 nm for excitation and emission, resp. The method has been validated in the 2-100 ng/mL-range, 2 ng/mL being the lower limit of quantification. Precision and accuracy both meet the current requirements for a bioanal. assay. The identity of the 4'H2S reaction products of aplidine have been confirmed by mass spectrometric anal. Finally, the method has been employed for a pilot pharmacokinetic study of aplidine in mice which demonstrated its usefulness for pharmacol. research.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 45 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:390172 HCAPLUS
DOCUMENT NUMBER: 131:179449
TITLE: Mode of action of thiocoraline, a natural marine compound with anti-tumor activity
AUTHOR(S): Erba, E.; Bergamaschi, D.; Ronzoni, S.; Faretta, M.; Taverna, S.; Bonfanti, M.; Catapano, C. V.; Faircloth, G.; Jimeno, J.; D'Incalci, M.
CORPORATE SOURCE: Laboratory of Cancer Pharmacology, Department of Oncology, Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, 20157, Italy
SOURCE: British Journal of Cancer (1999), 80(7), 971-980
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thiocoraline, a new anticancer agent derived from the marine actinomycete Micromonospora marina, was found to induce profound perturbations of the cell cycle. On both LoVo and SW620 human colon cancer cell lines, thiocoraline caused an arrest in the G1 phase of the cell cycle and a decrease in the rate of S phase progression towards G2/M phases, as assessed by using bromodeoxyuridine/DNA biparametric flow cytometric anal. Thiocoraline does not inhibit DNA-topoisomerase II enzymes in vitro, nor does it induce DNA breakage in cells exposed to effective drug concns. The cell cycle effects observed after exposure to thiocoraline appear related to the inhibition of DNA replication. By using a primer extension assay it was found that thiocoraline inhibited DNA elongation by DNA polymerase α at concns. that inhibited cell cycle progression and clonogenicity. These studies indicate that the new anticancer drug thiocoraline probably acts

by inhibiting DNA polymerase α activity.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 46 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:300619 HCAPLUS
DOCUMENT NUMBER: 131:82490
TITLE: Bioanalysis of thiocoraline, a new marine antitumoral depsipeptide, in plasma by high-performance liquid chromatography and fluorescence detection
AUTHOR(S): Sparidans, Rolf W.; Henrar, Roland E. C.; Jimeno, Jose M.; Faircloth, Glynn; Floriano, Pablo; Beijnen, Jos H.
CORPORATE SOURCE: Faculty of Pharmacy, Department of Pharmaceutical Analysis, Utrecht University, Utrecht, 3584 CA, Neth.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 726(1 + 2), 255-260
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive bioanal. assay for thicoraline, an investigational marine anticancer agent, in plasma, based on reversed-phase liquid chromatog. and fluorescence detection, is reported. The proteins in the sample are precipitated by the addition of acetonitrile. After centrifugation, the supernatant is injected directly into the chromatograph. The analyte is quantified by fluorescence detection with excitation and emission at 365 and 540 nm, resp. The method has been validated in the 1-100 ng/mL range, 1 ng/mL being the lower limit of quantification. Precision and accuracy both meet the current requirements for a bio-anal. assay and are <15% at 1 ng/mL and ≤5% in the 5-100 ng/mL range. Plasma samples can be stored for at least 4 mo at -800C. Finally, the usefulness of this method for pharmacol. research was shown in a pilot study of the pharmacokinetics of thiocoraline in rats.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 47 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:69332 HCAPLUS
DOCUMENT NUMBER: 130:291176
TITLE: Cell cycle perturbations and apoptosis induced by isohomohalichondrin B (IHB), a natural marine compound
AUTHOR(S): Bergamaschi, D.; Ronzoni, S.; Taverna, S.; Faretta, M.; De Feudis, P.; Faircloth, G.; Jimeno, J.; Erba, E.; D'Incalci, M.
CORPORATE SOURCE: Cancer Pharmacology Laboratory, Department of Oncology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy
SOURCE: British Journal of Cancer (1999), 79(2), 267-277
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Isohomohalichondrin B (IHB), a novel marine compound with anti-tumoral activity, extracted from the Lissodendorix sponge, inhibits GTP binding to tubulin, preventing microtubule assembly. Cell cycle perturbations and apoptosis induced by IHB were investigated on selected human cancer cell lines by using flow cytometric and biochem.

techniques. Monoparameter flow cytometric anal. showed that 1 h IHB exposure caused a delayed progression through S-phase, a dramatic block in G2M phase of the cell cycle and the appearance of tetraploid cell population in LoVo, LoVo/DX, MOLT-4 and K562 cells. At 24 h after IHB exposure, the majority of cells blocked in G2M were in prophase as assessed by morphol. anal. and by the fact that they expressed high levels of cyclin A/cdc2 and cyclin B1/cdc2. At 48 h, all cells were tetraploid as assessed by biparameter cyclin A/DNA and cyclin B1/DNA content anal. Apoptotic death was detected in both leukemic MOLT-4 and K562 cells, which express wild-type and mutated p53 resp., when the cells were blocked in mitotic prophase. In conclusion, IHB is a novel potent anti-tumor drug that causes delayed S-phase progression, mitotic block, tetraploidy and apoptosis in cancer cell lines.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 48 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:765472 HCAPLUS
DOCUMENT NUMBER: 129:325669
TITLE: Quantitative determination of Eteinascidin 743 in human plasma by miniaturized high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry
AUTHOR(S): Rosing, H.; Hillebrand, M. J. X.; Jimeno, J. M.; Gomez, A.; Floriano, P.; Faircloth, G.; Henrar, R. E. C.; Vermorken, J. B.; Cvitkovic, E.; Bult, A.; Beijnen, J. H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Journal of Mass Spectrometry (1998), 33(11), 1134-1140
CODEN: JMSPFJ; ISSN: 1076-5174
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A method was developed for the determination of Ecteinascidin 743 (ET-743) using miniaturized liquid chromatog. (LC) coupled to an electrospray ionization sample inlet (TurbolonSpray) and 2 quadrupole mass analyzers (LC/ESI-MS/MS). Solid-phase extraction was used as a sample pretreatment procedure. Ecteinascidin 743 is a very potent anticancer compound and is administered in μg m-2 dosages, which demands special requirements in terms of sensitivity for the anal. method supporting clin. pharmacokinetic studies. Using conventional LC/UV, a lower limit of quantitation (LLQ) of 1 ng mL-1 plasma was reached using a 500 μL sample volume, but LC/ESI-MS/MS permitted an LLQ of 10 pg mL-1. The latter method was accurate and precise, and provided a broad linear concentration range of 0.010-2.50 ng mL-1.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 49 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:646497 HCAPLUS
DOCUMENT NUMBER: 130:32755
TITLE: In vitro activity of aplidine, a new marine-derived anti-cancer compound, on freshly explanted clonogenic human tumor cells and hematopoietic precursor cells
AUTHOR(S): Depenbrock, H.; Peter, R.; Faircloth, G. T.;

Manzanares, I.; Jimeno, J.; Hanauske, A. R.
CORPORATE SOURCE: Technische Universitat Munchen, Division of Hematology and Oncology, Department of Medicine, Munich, 81675, Germany
SOURCE: British Journal of Cancer (1998), 78(6), 739-744
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aplidine is a new marine anti-cancer depsipeptide isolated from the Mediterranean tunicate Aplidium albicans. We have evaluated its antiproliferative action against a variety of freshly explanted human tumor specimens. Concentration ranges of 0.01-1.0 μM and 0.0001-1.0 μM were used in short- and long-term exposure schedules resp. After exposure for 1 h in 49 evaluable specimens, aplidine showed a clear concentration-dependent anti-tumor effect. At 0.05 μM, 85% of the specimens were markedly inhibited. Continuous exposure for 21-28 days in 54 tumor specimens also led to a concentration-dependent activity relationship. Fifty per cent and 100% tumor inhibitions were achieved with 0.001 μM and 0.05 μM resp. A head to head evaluation assessing short vs continuous exposure was carried out, resulting in evidence of an activity-time of exposure relationship. Breast, melanoma and non-small-cell lung cancer appear to be sensitive to low concns. of aplidine. In addn,. the evaluation of the effects of aplidine on hematopoietic cells showed a concentration-dependent toxicity. However, under continuous exposure, active concns. induced mild bone marrow toxicity, indicating that a therapeutic window at marginally myelotoxic concns. might exist.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 50 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:565299 HCAPLUS
DOCUMENT NUMBER: 129:270190
TITLE: Ecteinascidin-743, a new marine natural product with potent antitumor activity on human ovarian carcinoma xenografts
AUTHOR(S): Valoti, Giorgio; Nicoletti, M. Ines; Pellegrino, Antonio; Jimeno, Jose; Hendriks, Hans; D'Incalci, Maurizio; Faircloth, Glynn; Giavazzi, Raffaella
CORPORATE SOURCE: Mario Negri Institute for Pharmacological Research, Bergamo, Italy
SOURCE: Clinical Cancer Research (1998), 4(8), 1977-1983
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antitumor activity of ecteinascidin (ET)-743, a novel marine natural product, was evaluated against a panel of human ovarian carcinoma xenografts characterized by different malignant behaviors and drug responsiveness in nude mice. These tumor models included three xenografts transplanted s.c. (HOC18, HOC22-S, and MNB-PTX-1) into nude mice, representing different levels of sensitivity to cisplatinum (DDP), which was used as reference drug for ovarian carcinoma, and two other xenografts (HOC22 and HOC8), which are highly malignant in the peritoneal cavity of nude mice, representing the growth pattern of this neoplasm. At the maximum tolerated dose of 0.2 mg/kg using an intermittent schedule of one i.v. injection every 4 days, ET-743 was

highly active against HOC22-S (sensitive to DDP), inducing long-lasting, complete regressions, and against HOC18 (marginally sensitive to DDP), inducing partial tumor regressions. Moreover, significant growth delay was observed in mice bearing late-stage HOC18 tumor (400-mg tumor weight; nonresponsive to DDP). ET-743, however, was not active against MNB-PTX-1, a tumor that is highly resistant to chemotherapy, including DDP. In the i.p. ovarian carcinoma xenograft model, ET-743 at the maximum tolerated dose induced complete tumor remissions in all mice bearing HOC22 tumor, with 25% histopathol. confirmed cures, and produced marginal tumor growth delay against HOC8. These results indicate that ET-743 is a potent drug against ovarian carcinoma xenografts, being equally as active or more efficacious than DDP in the same tumor line. Our findings with human ovarian carcinoma xenografts justify clin. assessment of this drug with this tumor target.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 51 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:467222 HCAPLUS
DOCUMENT NUMBER: 129:211157
TITLE: Analysis of Ecteinascidin 743, a new potent marine-derived anticancer drug, in human plasma by high-performance liquid chromatography in combination with solid-phase extraction
AUTHOR(S): Rosing, H.; Hillebrand, M. J. X.; Jimeno, J. M.; Gomez, A.; Floriano, P.; Faircloth, G.; Cameron, L.; Henrar, R. E. C.; Vermorken, J. B.; Bult, A.; Beijnen, J. H.
CORPORATE SOURCE: Dept. of Pharmacy and Pharmacology, Slotervaart Hospital/Netherlands Cancer Institute, Louwesweg 6, Amsterdam, 1066 EC, Neth.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1998), 710(1 + 2), 183-189
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A reversed-phase high-performance liquid chromatog. method has been developed and validated for the quantification of the novel anticancer drug Ecteinascidin 743 in human plasma. The sample pretreatment of the plasma samples involved a solid-phase extraction (SPE) on cyano columns. Propyl-p-hydroxybenzoate was added after the sample pretreatment to correct for variability in injection vols. The separation was performed on a Zorbax SB-C18 column (75+4.6 mm I.D., particle size 3.5 μm) with acetonitrile-25 mM phosphate buffer, pH 5.0 (70:30, volume/volume) as the mobile phase. The flow-rate was 1.0 mL/min and the eluent was monitored at 210 nm. The accuracies and precisions of the assay fall within ±15% for all quality control samples and within ±20% for the lower limit of quantitation, which was 1.0 ng/mL using 500 μl of plasma. The overall recovery of the sample pretreatment procedure for Ecteinascidin 743 was 87.0±5.9%. The drug was found to be stable in human plasma at -30°C for at least 2 mo. At room temperature Ecteinascidin 743 was stable in human plasma for 5 h at most.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

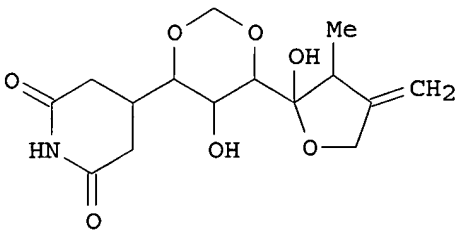
L20 ANSWER 52 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:100940 HCAPLUS
DOCUMENT NUMBER: 126:112679

TITLE: Progress in the acquisition of new marine-derived anticancer compounds: development of ecteinascidin-743 (ET-743)
AUTHOR(S): Jimeno, Jose M.; Faircloth, Glynn; Cameron, Lewis; Meely, Kathleen; Vega, Eduardo; Gomez, Andres; Sousa-Faro, Jose Ma Fernandez; Rinehart, Kenneth
CORPORATE SOURCE: Pharma Mar, S.A., Research and Development, Madrid, 28760, Spain
SOURCE: Drugs of the Future (1996), 21(11), 1155-1165
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 65 refs., of the progress in the acquisition of new marine-derived anticancer compds. and development of ecteinascidin-743 (ET-743).
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 53 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:590891 HCAPLUS
DOCUMENT NUMBER: 125:299492
TITLE: Immunosuppressive pharmaceutical compositions new biological activity from a marine Agrobacterium sp.
INVENTOR(S): Faircloth, Glynn T., Jr.; Millan, Francisco R.; Fernandez, Librada M. C.; Sarabia, Cristina A.
PATENT ASSIGNEE(S): Pharmamar, S.A., Spain
SOURCE: U.S., 13 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5556777	A	19960917	US 1993-118989	19930909
PRIORITY APPLN. INFO.:			US 1993-118989	19930909

GI



I

AB The active component of the pharmaceutical composition of the present invention is a compound which has been isolated from the controlled aerobic fermentation of a marine microorganism, Agrobacterium sp. PH-103. The pharmaceutical compns. of the present invention, useful for post surgical graft tolerance, are thus directed to compns. comprising a pharmaceutically acceptable carrier, diluent, or excipient and an effective amount of sesbanimide (I). I is an alkaloid that has been previously been isolated

from seeds and reported to be useful as an antitumor drug. Prior to the present invention however, this compound had not been isolated from any fermentation broth nor had it been determined to have immunomodulatory activity.

L20 ANSWER 54 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:356586 HCAPLUS
DOCUMENT NUMBER: 125:25629
TITLE: Structure-Activity Relationships of the Didemnins
AUTHOR(S): Sakai, Ryuichi; Kishore, Vimal; Kundu, Bijoy; Faircloth, Glynn; Gloer, James B.; Carney, John R.; Namikoshi, Michio; Sun, Furong; Hughes, Robert G., Jr.; et al.
CORPORATE SOURCE: Roger Adams Laboratory, University of Illinois, Urbana, IL, 61801, USA
SOURCE: Journal of Medicinal Chemistry (1996), 39(14), 2819-2834
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bioactivities of 42 didemnin congeners, either isolated from the marine tunicates Tridemnun solidum and Aplidium albicans or prepared synthetically and semisynthetically, were compared. The growth inhibition of various murine and human tumor cells and plaque reduction of HSV-1 and VSV grown on cultured mammalian cells were used to assess cytotoxicity and antiviral activity. Biochem. assays for macromol. synthesis (protein, DNA, and RNA) and enzyme inhibition (dihydrofolate reductase, thymidylate synthase, DNA polymerase, RNA polymerase, and topoisomerases I and II) were also performed to specify the mechanisms of action of each analog. Immunosuppressant activity of the didemnins was determined using a mixed lymphocyte reaction (MLR) assay. These assays revealed that the native cyclic depsipeptide core is an essential structural requirement for most of the bioactivities of the didemnins, especially for cytotoxicities and antiviral activities. The linear side-chain portion of the peptide can be altered with a gain, in some cases, of bioactivities. In particular, dehydrodidemnin B, tested against several types of tumor cells and in in vivo studies in mice, as well as didemnin M, tested for the mixed lymphocyte reaction and graft vs host reaction in murine systems, showed remarkable gains in their in vitro and in vivo activities compared to didemnin B.

L20 ANSWER 55 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:926111 HCAPLUS
DOCUMENT NUMBER: 123:340084
TITLE: Pyrrolo[3,2-e]indole derivatives, process for their preparation, and applications as antitumor agents
INVENTOR(S): Delamano Garcia, Jose; Tojo Suarez, Gabriel; Lopez Goti, Carmen; Fernandez Almeida, Jesus; Garcia Gravalos, Dolores; Faircloth, Glynn Thomas
PATENT ASSIGNEE(S): Universidad de Santiago de Compostela, Spain
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

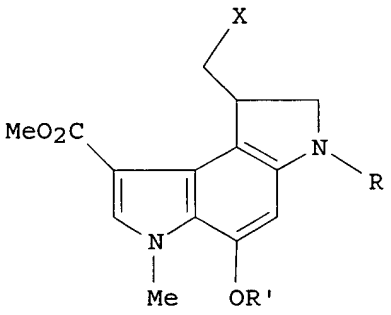
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9514022	A1	19950526	WO 1994-ES122	19941118
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
ES 2074957	A1	19950916	ES 1993-2430	19931119
ES 2074957	B1	19960616		
EP 680964	A1	19951108	EP 1995-900773	19941118
EP 680964	B1	20020116		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08509990	T2	19961022	JP 1994-514236	19941118
AT 212023	E	20020215	AT 1995-900773	19941118
PT 680964	T	20020628	PT 1995-900773	19941118
ES 2171521	T3	20020916	ES 1995-900773	19941118
US 5786377	A	19980728	US 1997-790904	19970129

PRIORITY APPLN. INFO.: ES 1993-2430 A 19931119; ES 1993-243 A 19930209; WO 1994-ES122 W 19941118; US 1996-491870 A1 19960515

OTHER SOURCE(S): CASREACT 123:340084; MARPAT 123:340084

GI



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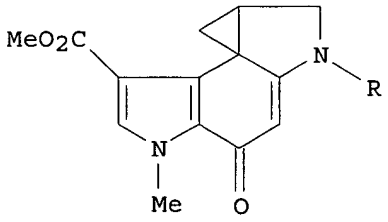
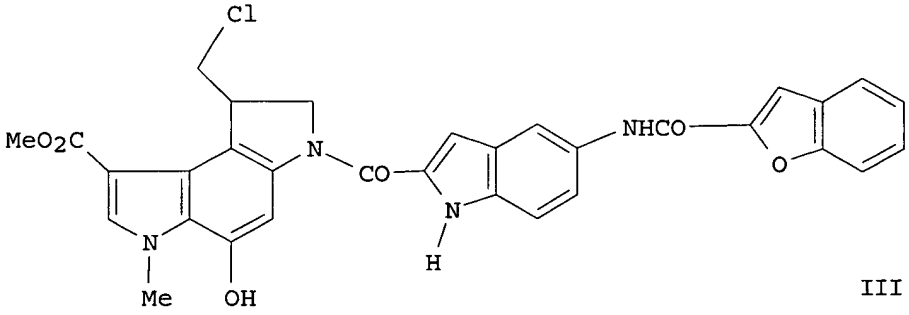


II



III

AB New pyrrolo[3,2-e]indole derivs. of formulas I and II are claimed [wherein R = COR''; R'' = (un)substituted aryl or heteroaryl; R' = H, (un)substituted alkanoyl, alkenoyl, alkynoyl, (hetero)arenocarbonyl; X = Cl, bromo, iodo, alkyl- or arylsulfonyl]. The compds. are prepared by: (a) deacetylating II (R = Ac) to give II (R = H); (b) subjecting the latter to a cyclopropyl ring-opening reaction to give I.HX (R = R' = H); (c) reacting this with an acid R''CO2H to yield I (R = COR'', R' = H); (d) optionally reacting I with a base in the presence of a condensing agent to obtain II; (e) optionally reacting I with a carboxylic acid in the

presence of a condensing agent or with an acid chloride in the presence of a base to give I (R' = acyl). I and II are useful as antitumor agents. For example, deacylation of II (R = Ac) with NaOMe in MeOH gave 99% II (R = H), which was cleaved by anhydrous HCl in EtOAc to give 93% I.HCl (R = R' = H, X = Cl). Coupling of this with 5-[(benzofuran-2-ylcarbonyl)amino]-1H-indole-2-carboxylic acid in DMF in the presence of EtN:C:N(CH2)3NMe2.HCl gave 69% title compound III. In the P388 tumor model in mice, III at 0.5 mg/kg/day i.p. for 9 days gave at treated/control survival ratio of > 391%.

L20 ANSWER 56 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:350780 HCAPLUS
DOCUMENT NUMBER: 122:114884
TITLE: Palau'amine: a pharmaceutical from a sponge (Stylotella agminata).
INVENTOR(S): Kinnel, Robin Bryan; Gehrken, Henning-Peter; Scheuer, Paul Joseph; Gravalos, Dolores Garcia; Faircloth, Glynn Thomas
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain
SOURCE: Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 626383	A1	19941130	EP 1994-302770	19940419
EP 626383	B1	19980916		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
CA 2121613	AA	19941021	CA 1994-2121613	19940419
ZA 9402686	A	19950721	ZA 1994-2686	19940419
AT 171180	E	19981015	AT 1994-302770	19940419
ES 2124844	T3	19990216	ES 1994-302770	19940419
AU 9460590	A1	19941027	AU 1994-60590	19940420
AU 672098	B2	19960919		
JP 07118274	A2	19950509	JP 1994-81870	19940420
JP 3489635	B2	20040126		
US 2002062023	A1	20020523	US 2001-928288	20010810
US 2002198379	A1	20021226	US 2002-184724	20020628
PRIORITY APPLN. INFO.:			GB 1993-8111 A	19930420
			US 1994-230389 B1	19940420
			US 2000-535900 B1	20000327
			US 2001-928288 B1	20010810

AB Palau'amine is isolated from a sponge (S. agminata). The compound may be used in the manufacture of pharmaceutical compns. for the treatment of tumors, fungal infections and as an immunosuppressant. The structure of the compound was determined and the compound was active against certain bacteria and fungi and tumors..

L20 ANSWER 57 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:150144 HCAPLUS
DOCUMENT NUMBER: 116:150144
TITLE: Immunosuppressant and antitumor acetylenic alcohols from Cribrochalina vasculum
INVENTOR(S): Gunasekera, Sarath P.; Faircloth, Glynn T.; Wright, Amy E.; Thompson, Winnie C.; Burres, Neal
PATENT ASSIGNEE(S): Harbor Branch Oceanographic Institution, Inc., USA
SOURCE: U.S., 6 pp.

CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5073572	A	19911217	US 1990-481475	19900216

PRIORITY APPLN. INFO.: US 1990-481475 19900216
OTHER SOURCE(S): MARPAT 116:150144

AB Five acetylenic alcs. with immunosuppressant and antitumor activity are isolated from C. vasculum and characterized. The alcs. displayed immunosuppressive activity in mixed lymphocyte reaction and CV-1 cytotoxicity assays. In vitro against P388 leukemia cells, and cells from human lung (A549) and colon (HT-29) tumors, these compds. had IC50s of 0.86-s.90 μg/mL.

L20 ANSWER 58 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:3685 HCAPLUS
DOCUMENT NUMBER: 114:3685
TITLE: New acetylenic alcohols from the sponge Cribrochalina vasculum
AUTHOR(S): Gunasekera, Sarath P.; Faircloth, Glynn T.
CORPORATE SOURCE: Div. Biomed. Mar. Res., Harbor Branch Oceanogr. Inst., Inc., Fort Pierce, FL, 34936, USA
SOURCE: Journal of Organic Chemistry (1990), 55(25), 6223-5
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Five new biol. active acetylenic alcs. were isolated from a sponge C. vasculum collected in Belize. Structures were determined by spectroscopic anal. with emphasis on 1H- and 13C-NMR data. All compds. showed immunosuppressive activity on in vitro mixed lymphocyte reaction tests and in vitro antitumor activity on mouse P388 tumor cell lines. This is the 1st report of branched aliphatic acetylenic compds. from marine organisms.

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